ABECMA (idecabtagene vicleucel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Abecma is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Chart notes, medical record documentation, or claims history supporting previous lines of therapy.

III. CRITERIA FOR INITIAL APPROVAL

Multiple Myeloma
Authorization of 3 months may be granted for treatment of relapsed or refractory multiple myeloma in members 18 years of age and older when all of the following criteria are met:

A. The member has received prior treatment with at least four prior lines of therapy, including at least one drug from each of the following categories:
    1. Immunomodulatory agent
    2. Proteasome inhibitor
    3. Anti-CD38 monoclonal antibody
B. The member has not received a previous treatment course of the requested medication or another CAR-T therapy directed at any target.
C. The member has an ECOG performance status of 0 to 2.
D. The member has adequate and stable kidney, liver, and cardiac function.
E. The member does not have known active or prior history of central nervous system (CNS) involvement (e.g., CNS multiple myeloma)
F. The member does not have clinically significant active infection.
G. The member does not have an active inflammatory disorder.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Abecma.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Multiple myeloma

4. National Coverage Determination: Chimeric Antigen Receptor (CAR) T-cell Therapy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Abecma are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

All FDA-approved indications are covered according to the conditions outlined in National Coverage Determination Manual section 110.24 (Chimeric Antigen Receptor [CAR] T-cell Therapy).

VI. REFERENCES

1. Abecma [package insert]. Summit, NJ: Celgene Corporation; March 2021.
2. National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24-Version 1). https://www.cms.gov/medicare-coverage-database/search.aspx. Accessed October 10, 2023.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Multiple Myeloma. Version 2.2024. Accessed December 14, 2023.
4. Patel U, Oluwole OO, Kassim A, et al. Sequencing bispecific antibodies and CAR T cell therapy in multiple myeloma with prior exposure to BCMA-targeted therapies. *J Clin Oncol*. 2023;41(16):e20049.

ABRAXANE (paclitaxel, albumin-bound)
paclitaxel, albumin-bound

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Metastatic Breast Cancer
   Indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

2. Non-Small Cell Lung Cancer
   Indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

3. Adenocarcinoma of the Pancreas
   Indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

B. Compendial Uses
1. Breast cancer
2. Non-small cell lung cancer
3. Pancreatic adenocarcinoma
4. Cutaneous melanoma
5. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
6. Kaposi sarcoma
7. Endometrial carcinoma
8. Biliary tract cancers: intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer
9. Uveal melanoma
10. Small bowel adenocarcinoma
11. Ampullary adenocarcinoma
12. Cervical cancer
13. Anal cancer
14. Gastric cancer
15. Head and neck cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Pancreatic adenocarcinoma
Authorization of 6 months may be granted for treatment of pancreatic adenocarcinoma, in combination with gemcitabine with or without cisplatin.

B. Breast cancer
Authorization of 6 months may be granted for treatment of breast cancer in any of the following settings:
1. Recurrent or metastatic disease

2. Following no response to preoperative systemic therapy
3. Neoadjuvant, in sequential combination with an anthracycline and cyclophosphamide
4. As a substitute for paclitaxel or docetaxel due to hypersensitivity reactions or contraindication to standard hypersensitivity premedications

C. Non-small cell lung cancer (NSCLC)

Authorization of 6 months may be granted for treatment of NSCLC in any of the following settings:

1. Recurrent, advanced or metastatic disease
2. As a substitute for paclitaxel or docetaxel due to hypersensitivity reactions or contraindication to standard hypersensitivity premedications

D. Cutaneous melanoma

Authorization of 6 months may be granted for subsequent treatment of metastatic or unresectable cutaneous melanoma, as a single-agent or in combination with carboplatin.

E. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer

Authorization of 6 months may be granted for treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer in any of the following settings:

1. Persistent or recurrent disease
2. As a substitute for paclitaxel due to a hypersensitivity reaction to paclitaxel

F. Kaposi sarcoma

Authorization of 6 months may be granted for treatment of Kaposi sarcoma.

G. Endometrial carcinoma

Authorization of 6 months may be granted for subsequent treatment of endometrial carcinoma, as a single agent.

H. Biliary tract cancers

1. Authorization of 6 months may be granted for treatment of unresectable, resected gross residual (R2), or metastatic intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma, in combination with gemcitabine with or without cisplatin.
2. Authorization of 6 months may be granted for treatment of gallbladder cancer in either of the following settings:
    i. Unresectable, resected gross residual (R2), or metastatic disease, in combination with gemcitabine with or without cisplatin
    ii. Neoadjuvant chemotherapy for resectable locally advanced disease, in combination with cisplatin and gemcitabine

I. Uveal melanoma

Authorization of 6 months may be granted for treatment of uveal melanoma, as single-agent therapy for metastatic or unresectable disease.

J. Small bowel adenocarcinoma

Authorization of 6 months may be granted for treatment of advanced or metastatic small bowel adenocarcinoma, as a single agent or in combination with gemcitabine.

K. Cervical cancer

Authorization of 6 months may be granted for subsequent treatment of persistent, recurrent, or metastatic cervical cancer, as a single agent.

L. Anal cancer

Authorization of 6 months may be granted for treatment of recurrent squamous cell carcinoma of the anal canal.

M. Gastric cancer

Authorization of 6 months may be granted for treatment of gastric cancer refractory to first-line fluoropyrimidine-containing chemotherapy.

N. Head and neck cancer
Authorization of 6 months may be granted for treatment of squamous cell carcinoma of the head and neck, including squamous cell carcinoma of the tongue.

O. Ampullary adenocarcinoma
Authorization of 6 months may be granted for treatment of ampullary adenocarcinoma, in combination with gemcitabine.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Abraxane and generic albumin-bound paclitaxel.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guidelines: Cervical cancer
4. NCCN Guidelines: Small bowel adenocarcinoma
5. NCCN Guidelines: Melanoma: Cutaneous
6. NCCN Guidelines: Kaposi sarcoma
7. NCCN Guidelines: Non-small cell lung cancer
8. NCCN Guidelines: Breast cancer
9. NCCN Guidelines: Melanoma: Uveal
10. NCCN Guidelines: Biliary tract cancers
11. NCCN Guidelines: Ovarian cancer including fallopian tube cancer and primary peritoneal cancer
12. NCCN Guidelines: Uterine neoplasms
13. NCCN Guidelines: Pancreatic adenocarcinoma
14. NCCN Guidelines: Ampullary adenocarcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Abraxane and generic albumin-bound paclitaxel are covered in addition to the following:
1. Breast cancer
2. Non-small cell lung cancer
3. Pancreatic adenocarcinoma
4. Cutaneous melanoma
5. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
6. Kaposi sarcoma
7. Endometrial carcinoma
8. Hepatobiliary cancers: intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer
9. Uveal melanoma
10. Small bowel adenocarcinoma
11. Ampullary adenocarcinoma
12. Cervical cancer

13. Anal cancer
14. Gastric cancer
15. Head and neck cancer

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Abraxane or albumin-bound paclitaxel to treat the below list of indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

1. Breast cancer
2. Non-small cell lung cancer
3. Pancreatic adenocarcinoma
4. Cutaneous melanoma
5. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
6. Kaposi sarcoma
7. Endometrial carcinoma
8. Hepatobiliary cancers: intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer
9. Uveal melanoma
10. Small bowel adenocarcinoma
11. Cervical cancer
12. Ampullary adenocarcinoma

Support for using Abraxane or albumin-bound paclitaxel to treat anal cancer, gastric cancer, and head and neck cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Abraxane [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; October 2022.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed January 17, 2024.
3. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: www.micromedexsolutions.com. Accessed January 24, 2024.
4. paclitaxel, albumin-bound [package insert]. Paramus, NJ: TWi Pharmaceuticals USA, Inc,; April 2022.

ACTEMRA (tocilizumab)
TOFIDENCE (tocilizumab-bavi)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs
2. Adult patients with giant cell arteritis
3. Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis
4. Patients 2 years of age and older with active systemic juvenile idiopathic arthritis
5. Adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) for slowing the rate of decline in pulmonary function
6. Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS)
7. Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

B. Compendial Uses
1. Rheumatoid arthritis with no previous treatment failure
2. Unicentric Castleman disease
3. Multicentric Castleman disease
4. Immunotherapy-related inflammatory arthritis
5. Acute graft versus host disease
6. Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
7. Thyroid eye disease

Note: The criteria outlined in this policy is only applicable to coverage in the outpatient setting. Hospitalized members receiving treatment of COVID-19 will be managed according to the member's inpatient benefit.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for systemic sclerosis-associated interstitial lung disease: For initial requests: Results of a chest high-resolution computed tomography (HRCT) study.

III. CRITERIA FOR INITIAL APPROVAL

A. Rheumatoid arthritis
Authorization of 12 months may be granted for treatment of rheumatoid arthritis.

B. Juvenile idiopathic arthritis
Authorization of 12 months may be granted for treatment of polyarticular or systemic juvenile idiopathic arthritis.

C. Giant cell arteritis

Authorization of 12 months may be granted for treatment of giant cell arteritis.

D. Systemic sclerosis-associated interstitial lung disease (SSc-ILD)
Authorization of 12 months may be granted for treatment of sclerosis-associated interstitial lung disease when the diagnosis was confirmed by a high-resolution computed tomography (HRCT) study of the chest.

E. Unicentric Castleman disease
Authorization of 12 months may be granted for treatment of unicentric Castleman disease when all of the following criteria are met:
1. The member is HIV-negative.
2. The member is human herpesvirus-8-negative.
3. The requested medication will be used as a single agent.
4. The disease has progressed following treatment of relapsed/refractory disease.

F. Multicentric Castleman disease
Authorization of 12 months may be granted for treatment of multicentric Castleman disease when both of the following criteria are met:
1. The requested medication will be used as a single agent.
2. The disease has progressed following treatment of relapsed/refractory or progressive disease.

G. Cytokine release syndrome
1. Authorization of 1 month may be granted for treatment of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS).
2. Authorization of 1 month may be granted for treatment of cytokine release syndrome in members with refractory CRS related to blinatumomab therapy.

H. Immunotherapy-related inflammatory arthritis
Authorization of 12 months may be granted for treatment of refractory or severe immunotherapy-related inflammatory arthritis that has not responded to systemic corticosteroids.

I. Acute graft versus host disease
Authorization of 12 months may be granted for treatment of acute graft versus host disease when either of the following criteria is met:
1. Member has experienced an inadequate response to systemic corticosteroids.
2. Member has an intolerance or contraindication to corticosteroids.

J. Thyroid Eye Disease
Authorization of 12 months may be granted for treatment of active Graves' orbitopathy that has not responded to corticosteroids.

IV. CONTINUATION OF THERAPY

A. Cytokine release syndrome, immunotherapy-related inflammatory arthritis, and acute graft versus host disease
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. Rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, and thyroid eye disease
All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when both of the following criteria are met:
1. The member is currently receiving therapy with Actemra or Tofidence.
2. The member is receiving benefit from therapy.

C. All other indications

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Actemra or Tofidence.
2. Actemra or Tofidence is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen AND
   ii. No evidence of disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Actemra and its biosimilar.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Hematopoietic cell transplantation
4. NCCN Guideline: Management of immunotherapy-related toxicities
5. NCCN Guideline: B-cell lymphomas
6. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Actemra are covered in addition to the following:
1. Rheumatoid arthritis with no previous treatment failure
2. Unicentric Castleman disease
3. Multicentric Castleman disease
4. Immunotherapy-related inflammatory arthritis
5. Acute graft versus host disease
6. Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
7. Thyroid eye disease

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using tocilizumab to treat rheumatoid arthritis with no previous treatment failure can be found in the FUNCTION trial (Burmester et al). In the randomized FUNCTION trial in methotrexate-naive patients with early rheumatoid arthritis (N=1162), a significantly greater proportion of patients receiving tocilizumab 8 mg/kg with methotrexate compared with methotrexate alone achieved remission evaluated with a Disease Activity Score using 28 joints and erythrocyte sedimentation rate (DAS28-ESR) of less than 2.6 at week 24 (45% vs 15%). Tocilizumab 8 mg/kg plus methotrexate was also associated with a significant sustained DAS28-ESR response rate at week 52 compared with methotrexate alone (49% vs 20%), as well as an American College of Rheumatology (ACR) criteria improvement of 20% (ACR20), 50% (ACR50), and 70% (ACR70), and significantly greater inhibition of joint damage. Tocilizumab 8 mg/kg alone was significantly better than methotrexate alone for DAS28-ESR remission at weeks 24 and 52, but there was no significant difference between the 2 treatments for any of the ACR responses. After 2 years in the FUNCTION trial, DAS28-ESR remission was reported in 47.6% of patients in the tocilizumab 8 mg/kg plus methotrexate group and 43.5% in the tocilizumab 8 mg/kg monotherapy group compared with 16% in the methotrexate monotherapy group. More patients in the tocilizumab 8 mg/kg plus methotrexate group and the tocilizumab 8 mg/kg monotherapy group compared with the methotrexate monotherapy group achieved ACR20 (65.2% and 61.6% vs 25.4%), ACR50 (57.6% and 53.1% vs 22%), and ACR70 (46.6% and 39.4% vs 17.4%); the mean change from baseline to 2 years in vander Heijde-modified total Sharp score (vdH mTSS) was 0.19 and 0.62 versus 1.88.

Support for using tocilizumab to treat unicentric and multicentric Castleman disease can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using tocilizumab to treat immunotherapy-related inflammatory arthritis can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline indicates tocilizumab should be considered as additional disease modifying antirheumatic therapy for the management of moderate or severe immunotherapy-related inflammatory arthritis if no improvement was noted after holding immunotherapy and treating with oral corticosteroids or if the provider was unable to taper corticosteroids.

Support for using tocilizumab to treat acute graft versus host disease can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of tocilizumab for acute graft-versus-host disease as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using tocilizumab to treat cytokine release syndrome can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline supports the adding of infliximab for the management of the following immunotherapy-related conditions:

1. Prolonged (more than three days) G1 cytokine release syndrome (CRS) in patients with significant symptoms, comorbidities, and/or in elderly patients
2. CRS symptoms that persist for more than 24 hours in patients who have been treated with axicabtagene ciloleucel or brexucabtagene autoleucel
3. G1 CRS that develops less than 72 hours after infusion in patients who have been treated with lisocabtagene maraleucel
4. G2-G4 CRS
5. G1-G4 neurotoxicity as additional single-dose therapy if concurrent CRS

Support for using tocilizumab to treat cytokine release syndrome can be found in the National Comprehensive Cancer Network's guideline for acute lymphoblastic leukemia. The NCCN Guideline for acute lymphoblastic leukemia indicates tocilizumab can be considered as supportive care for patients with severe cytokine release syndrome related to blinatumomab therapy.

Support for using tocilizumab to treat thyroid eye disease can be found in the 2021 European Group on Grave's orbitopathy (EUGOGO) clinical practice guidelines. Tocilizumab can be used as second-line treatment for patients with moderate to severe and active Graves' orbitopathy (GO) unresponsive to first-line therapy. In patients with glucocorticoid-resistant disease, tocilizumab should be considered as treatment may rapidly resolve inflammatory signs. Methylprednisolone IV in combination with oral mycophenolate sodium (or mofetil) is first-line treatment.

VII. REFERENCES

1. Actemra [package insert]. South San Francisco, CA: Genetech, Inc.; December 2022.
2. Tofidence [package insert]. Cambridge, MA: Biogen MA Inc.; September 2023.
3. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 12, 2023.
4. National Comprehensive Cancer Network. The NCCN Drugs & Biologics Compendium. https://www.nccn.org. Accessed January 12, 2023.
5. Burmester GR, Rigby WF, van Vollenhoven RF, et al: Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016; 75(6):1081-1091.
6. Burmester GR, Rigby WF, van Vollenhoven RF, et al: Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naive patients with early rheumatoid arthritis: 2-year clinical and radiographic results from the randomised, placebo-controlled FUNCTION trial. Ann Rheum Dis 2017; 76(7):1279-1284.

7. Bartalena L, Kahaly GJ, Baldeschi L, et al: The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021; 185(4):G43-G67.

ACTHAR GEL (repository corticotropin injection)
PURIFIED CORTROPHIN GEL (repository corticotropin injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Acthar Gel:
      a. **Infantile Spasms:** as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age
      b. **Multiple Sclerosis:** treatment of acute exacerbations of multiple sclerosis in adults
      c. **Rheumatic Disorders:** as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis
      d. **Collagen Diseases:** during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)
      e. **Dermatologic Diseases:** severe erythema multiforme, Stevens-Johnson syndrome
      f. **Allergic States:** serum sickness
      g. **Ophthalmic Diseases:** severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
      h. **Respiratory Diseases:** symptomatic sarcoidosis
      i. **Edematous State:** to induce a diuresis or a remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus

   2. Purified Cortrophin Gel:
      a. **Rheumatic Disorders**: as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis; acute gouty arthritis.
      b. **Collagen Diseases**: during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).
      c. **Dermatologic Diseases**: severe erythema multiforme (Stevens-Johnson syndrome), severe psoriasis
      d. **Allergic States**: atopic dermatitis, serum sickness
      e. **Ophthalmic Diseases**: severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
      f. **Respiratory Diseases**: symptomatic sarcoidosis
      g. **Edematous States**: to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus
      h. **Nervous system**: acute exacerbation of multiple sclerosis

B. Compendial Uses:
   1. Diagnostic testing of adrenocortical function
   2. Acquired epileptic aphasia
   3. Gout

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. For multiple sclerosis, nephrotic syndrome, rheumatic disorders, collagen diseases, dermatologic diseases, ophthalmic diseases, symptomatic sarcoidosis, and allergic states: chart notes detailing the outcome of the most recent trial with glucocorticoids, including dosage and duration of treatment.
B. For gout: chart notes detailing the outcome of the most recent trial with a first-line treatment option (e.g., colchicine, nonsteroidal anti-inflammatory drug [NSAIDs], or glucocorticoids), including dosage and duration of treatment.

III. EXCLUSIONS

A. Coverage of Purified Cortrophin Gel for the treatment of infantile spasms will be excluded.
B. Coverage of Acthar Gel for acute gouty arthritis, severe psoriasis, allergic conjunctivitis, and atopic dermatitis will be excluded.
C. Use of Acthar Gel in combination with Purified Cortrophin Gel will be excluded.

IV. CRITERIA FOR INITIAL APPROVAL

A. Infantile Spasms (Acthar Gel only)
Authorization of 6 months may be granted for treatment of infantile spasms in members who are less than 2 years of age.

B. Multiple Sclerosis
Authorization of 3 weeks may be granted for treatment of acute exacerbations of multiple sclerosis when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

C. Nephrotic Syndrome
Authorization of 3 months may be granted for treatment of nephrotic syndrome when repository corticotropin is requested for induction of diuresis or for remission of proteinuria in a member who has had an inadequate response to a trial of parenteral or oral glucocorticoids.

D. Rheumatic Disorders
Authorization of 3 months may be granted to members who are prescribed repository corticotropin as adjunctive treatment for rheumatic disorders (e.g., psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

E. Collagen Diseases
Authorization of 3 months may be granted for treatment of collagen diseases (e.g., systemic lupus erythematosus, systemic dermatomyositis, polymyositis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

F. Dermatologic Diseases
Authorization of 3 months may be granted for treatment of dermatologic disorders (e.g., severe erythema multiforme, Stevens-Johnson syndrome, severe psoriasis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

G. Ophthalmic Diseases
Authorization of 3 months may be granted for treatment of ophthalmic diseases (e.g., allergic conjunctivitis, keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation) when the member has had an inadequate response to a trial of parenteral, oral, or topical ophthalmic glucocorticoids.

H. Symptomatic Sarcoidosis
Authorization of 3 months may be granted for treatment of symptomatic sarcoidosis when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

I. Allergic States
Authorization of 1 month may be granted for treatment of allergic states (e.g., atopic dermatitis, serum sickness) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

J. Diagnostic Testing of Adrenocortical Function
Authorization of 1 dose may be granted to members who are prescribed repository corticotropin for diagnostic testing of adrenocortical function when the member cannot be tested with Cosyntropin.

K. Acquired Epileptic Aphasia
Authorization of 3 months may be granted for treatment of acquired epileptic aphasia.

L. Gout
Authorization of 1 month may be granted for treatment of acute gout attack when the member has had an inadequate response with a first-line treatment option (e.g., colchicine, NSAIDs, or glucocorticoids).

V. CONTINUATION OF THERAPY

A. Infantile Spasms (Acthar Gel only)
All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Acthar Gel
2. The member is receiving benefit from therapy.

B. All Other Indications
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Acthar Gel and Purified Cortrophin Gel.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Infantile spasms: A U.S. consensus report.
4. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society
5. Treatment of infantile spasms- a Cochrane Database Systematic Review
6. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis- a Cochrane Database Systematic Review
7. EFNS guidelines on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis
8. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis
9. KDIGO clinical practice guideline for glomerulonephritis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Acthar Gel and Purified Cortrophin Gel are covered in addition to the following:
1. Diagnostic testing of adrenocortical function
2. Acquired epileptic aphasia
3. Gout

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Acthar Gel or purified Cortrophin Gel to treat multiple sclerosis after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in several published studies.
Thompson and colleagues compared the efficacy of high-dose intravenous methylprednisolone with intramuscular ACTH in the treatment of acute relapse in multiple sclerosis in a double-blind, randomized, controlled study involving 61 patients. There was a marked improvement in both groups in the course of the study, but no difference between them in either the rate of recovery or the final outcome. High-dose IV methylprednisolone is a safe alternative to ACTH in the management of acute relapse in multiple sclerosis. Additionally, Berkovich and Agius indicate that while high-dose methylprednisolone is recommended to induce a faster recovery from a clinical exacerbation, ACTH is an alternative for patients who do not respond to or tolerate corticosteroids.
Frohman et al published an article discussing the treatment of MS exacerbations. They state ACTH is an alternative approach to intravenous methylprednisolone. ACTH was noted to be more expensive than steroids, have more side effects, and gives less consistent results. ACTH can be used when a patient is unresponsive to corticosteroids or in cases in which ACTH's positive effects on bone via stimulation of dehydroepiandrosterone and mineralocorticoids may be desirable.

Support for using Acthar Gel or purified Cortrophin Gel to treat nephrotic syndrome after an in adequate response to a trial of parenteral or oral glucocorticoids can be found in a prospective trial by Bomback and colleagues. Fifteen subjects with resistant glomerular diseases were treated with ACTH gel (80 units subcutaneously twice weekly) for 6 months. Resistant membranous nephropathy (MN), minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS) were defined as failure to achieve sustained remission of proteinuria off immunosuppressive therapy with at least 2 treatment regimens (one of which was a corticosteroid); resistant IgA nephropathy was defined as >1 g/g urine protein:creatinine ratio despite maximally tolerated RAAS blockade. Remission was defined as stable or improved renal function with ≥50% reduction in proteinuria to <0.5 g/g (complete remission) or 0.5-3.5 g/g (partial remission). The study included 5 subjects with resistant idiopathic MN, 5 subjects with resistant MCD (n = 2)/FSGS (n = 3), and 5 subjects with resistant IgA nephropathy. Two resistant MN subjects achieved partial remission on ACTH therapy, although 3 achieved immunologic remission of disease (PLA(2)R antibody disappeared by 4 months of therapy). One subject with resistant FSGS achieved complete remission on ACTH; one subject with resistant MCD achieved partial remission but relapsed within 4 weeks of stopping ACTH. Two subjects with resistant IgA nephropathy demonstrated >50% reductions in proteinuria while on ACTH, with proteinuria consistently <1 g/g by 6 months. Three of 15 subjects reported significant steroid-like adverse effects with ACTH, including weight gain and hyperglycemia, prompting early termination of therapy without any clinical response.

Support for using Acthar Gel or purified Cortrophin Gel to treat rheumatic disorders after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in the package insert and several guidelines. In the 2012 American College of Rheumatology Guidelines for Management of Gout, ACTH should be used in patients unable to take oral corticosteroids as an alternative to intra-articular, intravenous, or intramuscular corticosteroids.

Support for using Acthar Gel or purified Cortrophin Gel to treat collagen diseases after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in a published retrospective case series by Levine. Five patients were described, all of whom received oral or parenteral corticosteroids prior to using ACTH. The patients tolerated ACTH for up to three months with no significant side effects and no need to taper therapy. The author concludes that ACTH should be considered as an option for refractory dermatomyositis and polymyositis.
Patel and colleagues (2016) stated that idiopathic inflammatory myopathies are a group of systemic autoimmune diseases that involve inflammation of skeletal muscle. The 2 most common forms are dermatomyositis and polymyositis, the former of which entails a skin component. There are few approved therapeutics available for treatment of this group of diseases and the first-line therapy is usually corticosteroid treatment. Considering that a large proportion of patients do not respond to or cannot tolerate corticosteroids, additional treatments are needed. There are second-line therapies available, but many patients are also refractory to those options. H.P. Acthar Gel (repository corticotropin injection [RCI]) is a melanocortin peptide

that can induce steroid-dependent effects and steroid-independent effects. These researchers presented a series of cases that involved the use of RCI in the management of dermatomyositis and polymyositis; RCI treatments resulted in improvement in 3 of 4 patients, despite failure with previous therapies. The use of RCI did not exacerbate any co-morbidity and no significant changes in blood pressure, weight, or glycemic control were observed. The authors concluded that these findings were encouraging and suggested that RCTs applying RCI to dermatomyositis and polymyositis are needed.
In an open-label, clinical trial, Aggarwal and colleagues (2018) evaluated the safety, efficacy, tolerability and steroid-sparing effect of RCI in refractory adult polymyositis (PM) and dermatomyositis (DM). Adults with refractory PM and DM were enrolled by 2 centers. Inclusion criteria included refractory disease defined as failing glucocorticoid and/or greater than or equal to 1 immunosuppressive agent, as well as active disease defined as significant muscle weakness and greater than 2 additional abnormal core set measures (CSMs) or a cutaneous 10 cm visual analog scale (VAS) score of greater than or equal to 3 cm and at least 3 other abnormal CSMs. All patients received RCI of 80 units subcutaneously twice-weekly for 24 weeks. The primary end-point was the International Myositis Assessment and Clinical Studies definition of improvement. Secondary end-points included safety, tolerability, steroid-sparing as well as the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism myositis response criteria (EULAR); 10 of the 11 enrolled subjects (6 DM, 4 PM) completed the study; 7 of 10 met the primary end-point of efficacy at a median of 8 weeks. There was a significant decrease in prednisone dose from baseline to conclusion (18.5 (15.7) versus 2.3 (3.2); $p < 0.01$). Most individual CSMs improved at week 24 compared with the baseline, with the muscle strength improving by greater than 10% and the physician global by greater than 40%; RCI was considered safe and tolerable. No patient developed significant weight gain or an increase of hemoglobin A1c or Cushingoid features. The authors concluded that treatment with RCI was effective in 70% of patients, safe and tolerable, and led to a steroid dose reduction in patients with adult myositis refractory to glucocorticoid and traditional immunosuppressive drugs. This was an open-label study with small sample size (n = 10); these preliminary findings need to be validated in well-designed studies.

Support for using Acthar Gel or purified Cortrophin Gel to treat dermatologic diseases after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in a case series. Brown (2016) stated that although numerous therapeutic options are available for patients with psoriatic arthritis (PsA), a need for effective and tolerable treatments remains for patients with refractory disease who have failed previous therapies and continue to experience tender and/or swollen joints, pain, and disease activity. Repository corticotropin injection is believed to produce steroidogenic, steroid-independent, anti-inflammatory, and immunomodulatory effects in patients with rheumatic disorders, such as PsA. Limited literature exists on the use of RCI in patients with refractory PsA. In a case-series study, this investigator provided information on the clinical features of patients with refractory PsA and their response to RCI. A total of 9 patients treated with RCI for refractory PsA were retrospectively identified and included in the case series. All 9 patients experienced at least transient improvements in their active skin and joint disease. In some patients, it was necessary to titrate the RCI to an appropriate dose; RCI was used in some patients to bridge with another PsA therapy, such as apremilast or certolizumab; RCI was well-tolerated but discontinued in 3 patients due to pre-existing conditions (hypertension and hyperglycemia). The author concluded that RCI may be a safe and effective option for patients with refractory PsA who failed therapy with multiple previous treatments. These preliminary findings need to be validated by well-designed studies.

Support for using Acthar Gel or purified Cortrophin Gel to treat ophthalmic disease after a trial of parenteral, oral or topical ophthalmic glucocorticoids can be found in a phase four, multicenter, open-label study. Wirta et al (2022) stated that non-infectious keratitis is a painful corneal inflammation treated with topical cyclosporine and other immunosuppressants. Additional therapeutic options are needed for keratitis that does not improve with standard therapies. In an open-label, multi-center, phase-IV clinical trial, these researchers examined the safety and effectiveness of RCI for the treatment of refractory severe non-infectious keratitis. Patients were 18 years of age or older with persistent severe keratitis despite treatment with topical immunosuppressants. Patients received 80 U of RCI subcutaneously twice-weekly for 12 weeks followed by a 4-week taper. Assessments included all domains of the Impact of Dry Eye on Everyday Life (IDEEL) Questionnaire, Ocular Discomfort and 4-Symptom Questionnaire, and VAS. Corneal fluorescein and conjunctival lissamine green staining, Conjunctival Redness Scale, Schirmer's test, VA, slit lamp examination, and IOP were also examined. Safety was evaluated via treatment-related AEs. Analyses were carried out using the modified intent-to-treat (mITT) population (patients who received 1 dose or more of RCI and contributed any post-baseline effectiveness data). In the mITT population (n = 35), 50.0% (95% confidence interval [CI]: 33.2% to 66.8%) of patients experienced clinically important improvements in the symptom bother domain of the IDEEL Questionnaire at week 12 of RCI therapy. All domains of the IDEEL and the Ocular Discomfort and 4-Symptom Questionnaire showed improvements at week 12 of RCI treatment. The most pronounced

improvements in the VAS at week 12 were for eye dryness and eye discomfort. Corneal staining, conjunctival staining, conjunctival redness, and tear production showed early improvements that were sustained through week 12. No new safety signals for RCI were identified. The authors concluded that RCI was safe and effective for refractory severe non-infectious keratitis that has not improved with other approved therapies.

These researchers stated that the findings of this study added to the body of literature for a condition that is still being examined extensively. They noted that drawbacks of this study included a relatively small sample size (n = 35), a short treatment period of 12 weeks, and a lack of a placebo comparator. However, because the patients were not permitted to receive standard therapies such as cyclosporine, lifitegrast, and corticosteroids during the study period, the observed improvements in the symptoms of keratitis were likely the result of RCI treatment. Moreover, these investigators stated that although the open-label study design was appropriate for this target population of patients with severe refractory keratitis, the safety and effectiveness of this treatment warrant further investigation in a randomized, placebo-controlled trial.
Additionally, Anesi and colleagues (2023) examined if subcutaneous RCI (Acthar gel) could be an effective potential therapeutic agent for non-infectious retinal vasculitis. Patients with active retinal vasculitis were followed with serial ultra-wide-field fluorescein angiograms and treated with 80 units of subcutaneous repository corticotropin injection twice-weekly. Primary outcome of greater than or equal to 50 % improvement in response level (RL) for retinal vasculitis and percent improvement in retinal vasculitis severity scoring (RVSS) by more than one quartile (greater than or equal to 25 %) at week 12 was met in 15 and 16 of the 30 total eyes, respectively, including 1 eye with severe retinal vasculitis in each group. Complete resolution of retinal vasculitis was observed in 7 eyes with a mean time of 17.1 weeks. Intra-ocular pressure (IOP) elevation requiring therapy and cataract progression were noted in 2 and 3 eyes, respectively; 1 patient stopped medication due to side effects (injection site reaction). The authors concluded that repository corticotropin injection was well-tolerated overall; it may be an effective therapeutic agent in the treatment of non-infectious retinal vasculitis. Moreover, these researchers stated that these findings should be validated with further well-designed studies with larger sample sizes.

The authors stated that this study had several drawbacks, which include its open-label status, a limited study period of only 24 weeks, the lack of a control population, varied etiology and severity of disease, concomitant use of other immunomodulatory medications, as well as the use of subjects either on or off these other forms of therapy. Participants of this study represented a variable group of disease processes that had retinal vasculitis, as might be expected in a condition or population being studied where the number of patients is few. Criticism could be made to this point of the validity of any conclusions brought forth in this study, however, with the etiology of these processes being at least agreeably non-infectious in nature, these investigators expected that these data contain merit in the way of an observed response of a non-infectious inflammatory process to a single given therapy. Lastly, although this trial was carried out with funding provided by “Mallinckrodt Pharmaceuticals, Bedminster, NJ”, the authors were solely responsible for protocol development, initiation of patient recruitment, administration of study protocol, as well as manuscript production.

Support for using Acthar Gel or purified Cortrophin Gel to treat symptomatic sarcoidosis after an inadequate trial or parenteral or oral glucocorticoids can be found in a study by Chopra and colleagues (2019). The authors stated that RCI (repository corticotropin injection) has regulatory approval for many indications, including symptomatic sarcoidosis. This large case-series study of patients with advanced symptomatic sarcoidosis treated with RCI described patient characteristics, utilization patterns, concomitant therapies, and physicians' assessments of treatment response. This trial included patients greater than or equal to 18 years of age and with symptomatic sarcoidosis who were treated with RCI in the previous 36 months and had completed a course of RCI or received RCI for greater than or equal to 6 months at the time of data collection. The study included 302 patients (mean age of 51 years; 52%, women) with a mean 4.8 years since initial diagnosis of sarcoidosis. Most patients (76%) had extra-pulmonary involvement, primarily in the skin (28%), joints (25%), heart (22%), and eyes (22%); 34% had multiple (greater than or equal to 2) organ involvement. The mean duration of RCI treatment was 32.5 weeks, with 61.6% of patients continuing RCI therapy for greater than or equal to 6 months. The RCI utilization pattern indicated an individualized approach to therapy, with a higher starting dose associated with a shorter duration of therapy compared with a lower starting dose. The percentage of patients who used corticosteroids decreased from 61.3% during the 3 months before initiation of RCI to 12.9% 3 months following RCI therapy; the mean daily dose of corticosteroid decreased from 18.2 mg to 9.9 mg. The proportion of patients given less than 10 mg/day of prednisone increased from 21% before RCI use to 47% 3 months after RCI use. According to physicians' assessments of change in patients' health status following RCI therapy, overall status improved in 95 % of patients, overall symptoms in 73%, lung function in 38%, and inflammation in 33%. The authors concluded that these findings suggested

that RCI is a viable therapeutic option for patients with advanced symptomatic sarcoidosis and provided insights on patient characteristics and practice patterns to help clinicians determine appropriate use.

The authors stated that this study was limited by its reliance on data retrospectively collected via a survey of respondents who had access to patient medical records, which might have had errors and omissions. These investigators tried to minimize the impact of potential missing data by focusing on patients' clinical aspects and physicians' assessments, the types of information that are usually readily available in medical records or best known to the respondents who submitted data for this study. The study did not quantify patients' outcomes such as diagnostic measurements and safety end-points. Furthermore, because of its inherent retrospective design, there may be a risk of bias, resulting in over-estimation of the effectiveness of RCI based on physicians' assessments. Because this was an exploratory and hypothesis-generating study, these researchers did not make any comparisons between RCI and a control group or other treatments, which may also result in bias. It is important to note the following: RCI is indicated for symptomatic sarcoidosis; RCI is included in treatment guidelines from the Foundation for Sarcoidosis Research; and a randomized, phase-IV, double-blind, placebo-controlled clinical trial is ongoing to examine the safety and efficacy of Acthar gel in patients with pulmonary sarcoidosis. Another limitation was the use of the physicians' assessments of improvement in a patient's health status as a key descriptive end-point to evaluate RCI therapy. This subjective end-point relied on each individual physician's interpretation of each patient's medical record and the physician's standards for assessing improvement. These researchers did not collect data on test results or other objective measures that physicians might have used to make their determinations. The retrospective and non-comparative study design did not allow the authors to discern whether patients were responding to known concomitant treatments or to therapies not known to the physician or not recorded in the medical records. The use of physicians' assessment may have under-estimated the use of biologics in these patients; however, this could not be fully ascertained from the present study.

Support for using parenteral or oral glucocorticoids be found in several guidelines and the package insert. The American Academy of Allergy, Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology state systemic corticosteroids orally or intravenous may be necessary in severe cases of serum sickness. For atopic dermatitis, the American Academy of Dermatology and European guidelines for the treatment of atopic dermatitis (2018) both agree using corticosteroids is acceptable for acute flares but long-term oral corticosteroids are not recommended.

Support for using Acthar Gel or purified Cortrophin Gel for diagnostic testing of adrenocortical function can be found in the American Hospital Formulary Service-Drug Information (AHFS-DI) reference. Acthar Gel and purified Cortrophin Gel can be used as an aid in the diagnosis of adrenocortical insufficiency. The 30-minute cosyntropin test provides a good method of screening for primary adrenocortical insufficiency (Addison's disease) and is preferable to corticotropin for rapid screening since it is less likely to cause allergic reactions. When a greater stimulus to the adrenal cortex is desired, corticotropin or cosyntropin may be administered by IV infusion. If subnormal increases in plasma cortisol concentrations occur following administration of corticotropin or cosyntropin, additional tests providing prolonged stimulation of the adrenal cortex are required before impaired adrenocortical function can be diagnosed precisely and differentiation between primary and secondary adrenocortical insufficiency can be established.

Support for using Acthar Gel or purified Cortrophin Gel to treat acquired epileptic aphasia can be found in a case study reported by Lerman, Lerman-Sagie, and Kivity. Corticotropin 80 units/day was given for 3 months; after 3 weeks of treatment electroencephalographic results improved and after 6 months speech returned. When after 2 years the aphasia recurred corticotropin was immediately reinstituted; within a few weeks speech and electroencephalogram returned to normal. Landau-Kleffner syndrome is a rare syndrome of childhood characterized by an acquired aphasia associated with abnormal electroencephalogram, with about two-thirds of cases also exhibiting seizure activity.

Support for using Acthar Gel or purified Cortrophin Gel to treat gout can be found the gout guidelines from the American College of Rheumatology. Colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or IM) are recommended as first-line treatment for gout flares over adrenocorticotropic hormone (ACTH). For patients who cannot take medications by mouth, glucocorticoids (IM, IV, or intraarticular) are recommended over ACTH, although subcutaneous synthetic ACTH is a suggested alternative.

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ADAKVEO (crizanlizumab-tmca)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Adakveo is indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Sickle cell disease, to reduce the frequency of vaso-occlusive crises
Authorization of 12 months may be granted for use in reducing the frequency of vaso-occlusive crises (VOCs) in members 16 years of age or older with sickle cell disease when both of the following criteria are met:
A. The member has experienced at least one vaso-occlusive crisis within the previous 12 months.
B. The member meets either of the following (1 or 2):
    1. Member has sickle hemoglobin C (HbSC) or sickle β^+-thalassemia (HbSβ^+) genotype.
    2. Member has homozygous hemoglobin S (HbSS) or sickle β^0-thalassemia (HbSβ^0) genotype AND meets any of the following:
        i. Has experienced, at any time in the past, an inadequate response or intolerance to a trial of hydroxyurea.
        ii. Has a contraindication to hydroxyurea.
        iii. Will be using Adakveo with concurrent hydroxyurea therapy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Adakveo.
B. Adakveo is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as reduction in the frequency of vaso-occlusive crises, or maintenance of such reduction, since initiating therapy with Adakveo.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Adakveo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Evidence-based management of Sickle Cell Disease (NHLBI)

4. Guidelines for the use of hydroxycarbamide in children and adults (2018 British Society for Haematology)
5. Hydroxyurea (hydroxycarbamide) for sickle cell disease (Cochrane Review)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Adakveo are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for requiring a trial and inadequate response, intolerance, or contraindication to hydroxyurea can be found in the National Heart, Lung, and Blood Institute (NHLBI) recommendations, the 2018 British Society of Haematology Guidelines, and a Cochrane Review.

The 2014 expert panel report from the NHLBI recommends treatment with hydroxyurea in adults with sickle cell anemia (SCA) who have had three or more moderate to severe sickle cell pain crises in the last 12 months, pain that interferes with daily activities and quality of life, history of severe and/or recurrent acute chest syndrome (ACS), severe symptomatic chronic anemia, and in infants nine months of age and older, children, and adolescents regardless of severity, to reduce complications. The report notes that SCA refers to HbSS or HbSbeta0 thalassemia, while SCD refers to all genotypes including SCA in addition to compound heterozygous disorders such as HbSC and HbSbeta+thalassemia. For individuals with HbSC and HBSbeta+thalassemia who have recurrent pain, the report recommends consideration of hydroxyurea in consultation with a sickle cell expert.

The 2018 British Society for Haematology guidelines for the use of hydroxyurea in SCD recommend the following for patients with HbSS or HbSbeta0 thalassemia:

- In infants who are nine to 42 months of age, hydroxyurea should be offered regardless of clinical severity to reduce sickle cell complications.
- In children older than 42 months of age, adolescents and adults, hydroxyurea should be offered in view of the impact on reduction of mortality.
- Adults and children should be treated with hydroxyurea if they have had three or more moderate to severe pain crisis in a 12-month period, have sickle cell pain that interferes with daily activities and quality of life, and have a history of severe and/or recurrent ACS.

For children and adults with genotypes other than HbSS or HbSbeta0 thalassemia, the guideline recommends consideration of hydroxyurea in those who have recurrent episodes of acute pain, ACS, or hospitalization.

A Cochrane Review by Rankine-Mullings and Nevitt included nine randomized controlled trials that evaluated the use of hydroxyurea in SCD. The RCTs enrolled a total of 1,104 adults and children with SCD (HbSS, HbSC or HbSbeta0 thalassemia genotypes). The authors found there is evidence that hydroxyurea may be effective in decreasing the frequency of pain episodes and other acute complications in adults and children with HbSS or HbSbeta0 thalassemia genotypes, and in preventing life-threatening neurological events in those at risk of primary stroke. The authors noted that evidence of the effects of hydroxyurea on individuals with the HbSC genotype is limited.

VI. REFERENCES

1. Adakveo [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2022.
2. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N *Engl J Med*. 2017;376(5):429-439.
3. Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014. National Institutes of Health. Available at https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease. Accessed July 5, 2023.
4. Qureshi A, Kaya B, Pancham S, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. *Br J Haematol*. 2018; 181(4):460-475.
5. Rankine-Mullings AE, Nevitt SJ. Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database Syst. Rev. 2022; 9(9):CD002202.

ADCETRIS (brentuximab vedotin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Classical Hodgkin Lymphoma (cHL)
      i. Treatment of cHL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
      ii. Treatment of cHL at high risk of relapse or progression as post-auto-HSCT consolidation
      iii. Previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine
      iv. Treatment of pediatric patients 2 years and older with previously untreated high risk classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide

   2. Systemic anaplastic large cell lymphoma (sALCL)
      i. Treatment of systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen
      ii. Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone
   3. Treatment of primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) in patients who have received prior systemic therapy

B. Compendial Uses
   1. cHL stage I-II unfavorable
   2. CD30+ B-Cell Lymphomas
      i. Monomorphic post-transplant lymphoproliferative disorders (B-cell type)
      ii. Monomorphic post-transplant lymphoproliferative disorders (T-cell type)
      iii. Diffuse large B-cell lymphoma
      iv. HIV-Related B-cell lymphomas (CD30+ HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma)
      v. High-grade B-Cell lymphomas
      vi. Primary mediastinal large B-cell lymphoma
   3. CD30+ Primary Cutaneous Lymphomas
      i. Mycosis Fungoides (MF)/Sezary Syndrome (SS)
      ii. Lymphomatoid papulosis (LyP)
      iii. Cutaneous anaplastic large cell lymphoma
   4. CD30+ T-Cell Lymphomas
      i. Hepatosplenic T-cell lymphoma
      ii. Adult T-cell leukemia/lymphoma
      iii. Breast implant-associated anaplastic large cell lymphoma (ALCL)
      iv. Peripheral T-cell lymphoma (PTCL)
      v. Extranodal NK/T-cell Lymphoma
      vi. Angioimmunoblastic T-cell lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Initial requests: Testing or analysis confirming CD30 expression on the surface of the cell

III. CRITERIA FOR INITIAL APPROVAL

A. Classical Hodgkin lymphoma (cHL)

Authorization of 12 months may be granted for treatment of CD30+ cHL when any of the following are met:

1. The requested drug will be used as a single agent, or
2. The requested drug will be used in combination with doxorubicin, vinblastine, and dacarbazine, or
3. The requested drug will be used in combination with bendamustine for subsequent therapy, or
4. The requested drug will be used in combination with dacarbazine, or
5. The requested drug will be used in combination with nivolumab for subsequent therapy,or
6. The requested drug will be used in combination with gemcitabine for subsequent therapy, or
7. The requested drug will be used in combination with ifosfamide, carboplatin and etoposide for subsequent therapy, or
8. The requested drug will be used in combination with etoposide, prednisone and doxorubicin, or
9. The requested drug will be used in combination with cyclophosphamide, prednisone, and dacarbazine for subsequent therapy, or
10. The requested drug will be used in combination with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide

B. B-Cell Lymphomas

Authorization of 12 months may be granted for treatment of CD30+ B-cell lymphomas with any of the following subtypes:

1. Monomorphic post-transplant lymphoproliferative disorders (B-cell type) when both of the following are met:
   i. The requested drug will be used for subsequent therapy, and
   ii. The member is not a candidate for transplant
2. Monomorphic post-transplant lymphoproliferative disorders (T-cell type) when the requested drug will be used in combination with cyclophosphamide, doxorubicin, and prednisone.
3. Diffuse large B-cell lymphoma when all of the following are met:
   i. The requested drug will be used as subsequent therapy, and
   ii. The member is not a candidate for transplant.
4. HIV-Related B-cell lymphomas (HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma) when both of the following are met:
   i. The requested drug will be used for subsequent therapy, and
   ii. The member is not a candidate for transplant.
5. High-grade B-cell lymphomas when both of the following are met:
   i. The requested drug will be used for subsequent therapy, and
   ii. The member is not a candidate for transplant.
6. Primary mediastinal large B-cell lymphoma when both of the following are met
   i. The requested drug will be used for relapsed or refractory disease, and
   ii. The requested drug will be used in combination with nivolumab or pembrolizumab

C. Primary Cutaneous Lymphomas

Authorization of 12 months may be granted for treatment of CD30+ primary cutaneous lymphomas with any of the following subtypes:

1. Mycosis fungoides (MF)/Sezary syndrome (SS)
2. Lymphomatoid papulosis (LyP) when both of the following are met:
   i. The requested drug will be used as a single agent, and

ii. The disease is relapsed or refractory.

3. Cutaneous anaplastic large cell lymphoma when either of the following are met:
   i. The requested drug will be used as a single agent, or
   ii. The requested drug will be used in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).

D. T-Cell Lymphomas

Authorization of 12 months may be granted for treatment of CD30+ T-cell lymphomas with any of the following subtypes:

1. Hepatosplenic T-cell lymphoma when either of the following are met:
   i. The requested drug will be used as a single agent after two or more primary treatment regimens, or
   ii. The requested drug will be used in combination with cyclophosphamide, doxorubicin, and prednisone.
2. Adult T-cell leukemia/lymphoma when either of the following are met:
   i. The requested drug will be used as a single agent for subsequent therapy, or
   ii. The requested drug will be used in combination with cyclophosphamide, doxorubicin, and prednisone.
3. Breast implant associated anaplastic large cell lymphoma (ALCL) when either of the following are met:
   i. The requested drug will be used as a single agent, or
   ii. The requested drug will be used in combination with cyclophosphamide, doxorubicin, and prednisone.
4. Peripheral T-cell lymphoma (PTCL) [including the following subtypes: anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma] when either of the following are met:
   i. The requested drug will be used a single agent for subsequent or palliative therapy, or
   ii. The requested drug will be used in combination with cyclophosphamide, doxorubicin, and prednisone.
5. Extranodal NK/T-cell lymphoma when all of the following are met:
   i. The requested drug will be used as a single agent, and
   ii. The member has relapsed or refractory disease, and
   iii. The member has had an inadequate response or contraindication to asparaginase-based therapy (e.g., pegaspargase).
6. Systemic anaplastic large cell lymphoma when either of the following are met:
   i. The requested drug will be used as a single agent, or
   ii. The requested drug will be used in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested drug.
B. The requested drug is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as:
   1. No evidence of unacceptable toxicity while on the current regimen and
   2. No evidence of disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Adcetris.
2. The available compendium

a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Hodgkin lymphoma
4. NCCN Guideline: T-cell lymphomas
5. NCCN Guideline: Pediatric Hodgkin lymphoma
6. NCCN Guideline: Pediatric aggressive mature B-cell lymphomas
7. NCCN Guideline: Primary cutaneous lymphomas
8. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Adcetris are covered in addition to the following:

1. cHL stage I-II unfavorable
2. CD30+ B-Cell Lymphomas
   i. Monomorphic post-transplant lymphoproliferative disorders (B-cell type)
   ii. Monomorphic post-transplant lymphoproliferative disorders (T-cell type)
   iii. Diffuse large B-cell lymphoma
   iv. HIV-Related B-cell lymphomas (CD30+ HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma)
   v. High-grade B-Cell lymphomas
   vi. Primary mediastinal large B-cell lymphoma
3. CD30+ Primary Cutaneous Lymphomas
   i. Mycosis Fungoides (MF)/Sezary Syndrome (SS)
   ii. Lymphomatoid papulosis (LyP)
   iii. Cutaneous anaplastic large cell lymphoma
4. CD30+ T-Cell Lymphomas
   i. Hepatosplenic T-cell lymphoma
   ii. Adult T-cell leukemia/lymphoma
   iii. Breast implant-associated anaplastic large cell lymphoma (ALCL)
   iv. Peripheral T-cell lymphoma (PTCL)
   v. Extranodal NK/T-cell Lymphoma
   vi. Angioimmunoblastic T-cell lymphoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for cHL stage I-II unfavorable can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for CD30+ B-cell lymphomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for CD30+ primary cutaneous lymphomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for CD30+ T-cell lymphomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-

cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Adcetris [package insert]. Bothell, WA: Seagen, Inc; November 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed April 5, 2023.

ADSTILADRIN (nadofaragene firadenovec-vncg)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Adstiladrin is indicated for the treatment of adult patients with high-risk Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

B. Compendial Use
Non-muscle invasive bladder cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Bladder Cancer
Authorization of 12 months may be granted for treatment of bladder cancer when all of the following criteria are met:
1. The member has non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) or high-grade papillary Ta/T1 tumor without CIS
2. The disease is high-risk
3. The disease is Bacillus Calmette-Guerin (BCG)-unresponsive

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease recurrence while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Adstiladrin.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Bladder cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Adstiladrin are covered in addition to high-risk NMIBC with high-grade papillary Ta/T1 tumors without CIS.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Adstiladrin to treat high-risk NMIBC with high-grade papillary Ta/T1 tumors without CIS can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Adstiladrin [package insert]. Kastrup, Denmark: Ferring Pharmaceuticals; December 2022.
2. The NCCN Drugs & Biologics Compendium™ © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org Accessed August 6, 2023.

ADUHELM (aducanumab-avwa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Aduhelm is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests:
    1. Medical records (e.g., chart notes) documenting the following:
        i. Diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.
    2. Presence of amyloid pathology documented by either of the following:
        i. Baseline positron emission tomography (PET) scan
        ii. Lumbar puncture results
    3. Current enrollment in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.
B. Continuation requests:
    1. Continued enrollment in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

III. CRITERIA FOR INITIAL APPROVAL

Alzheimer's Disease
Authorization of 6 months may be granted for treatment of Alzheimer's disease (AD) when all of the following criteria are met:
A. Member must have mild cognitive impairment due to AD or mild AD dementia.
B. Member must meet one of the following criteria:
    1. Have a positron emission tomography (PET) scan confirming the presence of amyloid pathology.
    2. Have results from a lumbar puncture confirming at least one of the following detected in cerebrospinal fluid (CSF) as determined by the lab assay:
        i. Presence of elevated phosphorylated tau (P-tau) protein and/or total tau (T-tau) protein, and reduced beta amyloid-42 (AB42)
        ii. Low AB42/AB40 ratio
        iii. Elevated P-Tau/AB42 ratio
        iv. Elevated T-Tau/AB42 ratio
C. Member must currently be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 6 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Aduhelm.
B. Aduhelm is being used to treat an indication enumerated in Section III.
C. The member continues to be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Aduhelm.
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology
3. National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aduhelm are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Using Aduhelm to treat mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease (AD) dementia is covered according to the conditions outlined in National Coverage Determination Manual section 200.3- Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Monoclonal antibodies directed against amyloid that are approved by the FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry.

VII. REFERENCES

1. Aduhelm [package insert]. Cambridge, MA: Biogen; February 2023.
2. National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (200.3 – Version 1). https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1 Accessed May 4, 2023.
3. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol. 2006;59(3):512-519.
4. Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimers Dement*. 2018;14(11):1460-1469.
5. Elecsys Phospho-Tau (181P) CSF 2022-12.

ADZYNMA (ADAMTS13, recombinant-krhn)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Adzynma is indicated for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: ADAMTS13 enzyme assay and ADAMTS13 genetic testing results supporting the diagnosis.
B. Continuation of therapy requests: Medical records (e.g., chart notes, lab reports) documenting a response to therapy (e.g., reduction or maintenance of number of thrombotic thrombocytopenic purpura [TTP] events, increase in platelet count, decrease in lactate dehydrogenase [LDH] level).

III. CRITERIA FOR INITIAL APPROVAL

Congenital thrombotic thrombocytopenic purpura (cTTP)
Authorization of 6 months may be granted for the treatment of congenital thrombotic thrombocytopenic purpura (cTTP) when both of the following criteria are met:
A. The diagnosis of cTTP has been confirmed by genetic testing with biallelic mutations in the ADAMTS13 gene.
B. Member has an ADAMTS13 activity level of less than 10% at the time of diagnosis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment of congenital thrombotic thrombocytopenic purpura (cTTP) when both of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The member is receiving benefit from therapy (e.g., reduction or maintenance of number of thrombotic thrombocytopenic purpura [TTP] events, increase in platelet count, decrease in lactate dehydrogenase [LDH] level).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Adzynma.
2. The available compendium

a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Adzynma are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using an enzyme assay and genetic testing to confirm the diagnosis of cTTP prior to initiating treatment with Adzynma can be found in the clinical trials cited in the prescribing information. To be included in the trial, the patient must have had a documented diagnosis of severe hereditary ADAMTS13 deficiency, defined as: A) Confirmed by molecular genetic testing, documented in participant history or at screening, and B) ADAMTS13 activity < 10 % as measured by the fluorescent resonance energy transfer- von Willebrand factor73 (FRETS-VWF73) assay, documented in participant history or at screening (participants currently receiving standard of care prophylactic therapy may exceed 10% ADAMTS13 activity at screening). Additionally, an article from The New England Journal of Medicine, cited in the prescribing information, indicates that hereditary TTP is caused by biallelic mutations in the gene ADAMTS13 that lead to a severe ADAMTS13 deficiency (ADAMTS13 activity <10% of that in normal plasma).

VII. REFERENCES

1. Adzynma [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; November 2023.
2. Asmis LM, Serra A, Krafft A, et al. Recombinant ADAMTS13 for Hereditary Thrombotic Thrombocytopenic Purpura. N Engl J Med 2022; 387: 2356-2361.

ALDURAZYME (laronidase)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Aldurazyme is indicated for adult and pediatric patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms.

Limitations of use:
- *The risks and benefits of treating mildly affected patients with the Scheie form have not been established.*
- *Aldurazyme has not been evaluated for effects on the central nervous system manifestations of the disorder.*

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: alpha-L-iduronidase enzyme assay and/or genetic testing results supporting diagnosis.
B. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

III. CRITERIA FOR INITIAL APPROVAL

Mucopolysaccharidosis I (MPS I)
Authorization of 12 months may be granted for treatment of MPS I when both of the following criteria are met:
A. Diagnosis of MPS I was confirmed by enzyme assay demonstrating a deficiency of alpha-L-iduronidase enzyme activity and/or by genetic testing.
B. Member has one of the following:
   1. The Hurler form (i.e., severe MPS I).
   2. The Hurler-Scheie form (i.e., attenuated MPS I).
   3. The Scheie form (Scheie syndrome; i.e., attenuated MPS I) with moderate to severe symptoms (e.g., normal intelligence, less progressive physical problems, corneal clouding, joint stiffness, valvular heart disease).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.

C. The member is receiving benefit from therapy. Benefit is defined as a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Aldurazyme.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aldurazyme are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assays or genetic testing prior to initiating Aldurazyme to treat MPS I can be found in a GeneReviews article (Clark LA). The diagnosis of MPS I can be established in one of two ways: detection of deficient activity of the lysosomal enzyme α-L-iduronidase (IDUA) in combination with elevation of glycosaminoglycan levels; and/or identification of biallelic pathogenic variants in IDUA on molecular genetic testing.

VII. REFERENCES

1. Aldurazyme [package insert]. Cambridge, MA: Genzyme Corporation; March 2023.
2. Wraith JE, Clarke LA, Beck M, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J Pediatr*. 2004;144:581-588.
3. Muenzer J, Wraith JE, Clarke LA; International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics. 2009 Jan;123(1):19-29.
4. Clarke LA. Mucopolysaccharidosis Type I. 2002 Oct 31 [Updated 2021 Feb 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Accessed January 3, 2024.

ALIQOPA (copanlisib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Aliqopa is indicated for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

B. Compendial Uses
1. Gastric MALT lymphoma (extranodal marginal zone lymphoma of the stomach), subsequent therapy for relapsed or refractory disease after 2 prior therapies
2. Non-gastric MALT lymphoma (extranodal marginal zone lymphoma of nongastric sites), subsequent therapy for relapsed or refractory disease after 2 prior therapies
3. Nodal marginal zone lymphoma, subsequent therapy as a single agent for relapsed or refractory disease after 2 prior therapies
4. Splenic marginal zone lymphoma, subsequent therapy as a single agent for relapsed or refractory disease after 2 prior therapies

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Follicular Lymphoma (FL)
Authorization of 12 months may be granted to members with follicular lymphoma (FL) when the requested medication will be used as subsequent therapy after at least two prior therapies.

B. Gastric MALT Lymphoma (Extranodal Marginal Zone Lymphoma of the Stomach) and Non-gastric MALT Lymphoma (Extranodal Marginal Zone Lymphoma of Nongastric Sites)
Authorization of 12 months may be granted to members with gastric or non-gastric mucosa-associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone lymphoma of the stomach and nongastric sites) when the requested medication will be used as subsequent therapy after at least two prior therapies.

C. Nodal Marginal Zone Lymphoma
Authorization of 12 months may be granted to members with nodal marginal zone lymphoma when the requested medication will be used as subsequent therapy after at least two prior therapies as a single agent.

D. Splenic Marginal Zone Lymphoma
Authorization of 12 months may be granted to members with splenic marginal zone lymphoma when the requested medication will be used as subsequent therapy after at least two prior therapies as a single agent.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen and
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Aliqopa.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aliqopa are covered in addition to the following:

1. Gastric MALT lymphoma (extranodal marginal zone lymphoma of the stomach), subsequent therapy for relapsed or refractory disease after 2 prior therapies
2. Non-gastric MALT lymphoma (extranodal marginal zone lymphoma of nongastric sites), subsequent therapy for relapsed or refractory disease after 2 prior therapies
3. Nodal marginal zone lymphoma, subsequent therapy as a single agent for relapsed or refractory disease after 2 prior therapies
4. Splenic marginal zone lymphoma, subsequent therapy as a single agent for relapsed or refractory disease after 2 prior therapies

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Aliqopa to treat gastric MALT lymphoma, non-gastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Aliqopa [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; March 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 2, 2023.

Alpha$_1$-Proteinase Inhibitors

ARALAST NP (alpha$_1$-proteinase inhibitor [human])
GLASSIA (alpha$_1$-proteinase inhibitor [human])
PROLASTIN-C (alpha$_1$-proteinase inhibitor [human])
ZEMAIRA (alpha$_1$-proteinase inhibitor [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. ARALAST NP
FDA-Approved Indication
Chronic augmentation therapy in adults with clinically evident emphysema due to severe congenital deficiency of alpha$_1$-proteinase inhibitor (alpha-antitrypsin deficiency)

B. GLASSIA
FDA-Approved Indication
Chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe hereditary deficiency of alpha$_1$-proteinase inhibitor (alpha$_1$-antitypsin deficiency)

C. PROLASTIN-C
FDA-Approved Indication
Chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of alpha$_1$- proteinase inhibitor (alpha$_1$- antitrypsin deficiency)

D. ZEMAIRA
FDA-Approved Indication
Chronic augmentation and maintenance therapy in adults with alpha$_1$-proteinase inhibitor (alpha$_1$-antitypsin) deficiency and clinical evidence of emphysema

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

Documentation of pretreatment serum alpha$_1$-antitrypsin (AAT) level must be available, upon request, for all submissions.

III. CRITERIA FOR INITIAL APPROVAL

Alpha$_1$-proteinase inhibitor (alpha$_1$-antitrypsin) deficiency
Authorization of 12 months may be granted for treatment of emphysema due to alpha$_1$-antitrypsin (AAT) deficiency when the member's pretreatment serum AAT level is less than 11 micromol/L (80 mg/dL by radial immunodiffusion or 50 mg/dL by nephelometry).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving alpha$_1$-proteinase inhibitor therapy.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with an alpha$_1$-proteinase inhibitor.
B. The alpha$_1$-proteinase inhibitor is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Aralast NP, Glassia, Prolastin-C, and Zemaira.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency.
4. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aralast NP, Glassia, Prolastin-C, and Zemaira are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the member's pretreatment serum AAT level is found in the guidelines published by the American Thoracic Society and Canadian Thoracic Society. Alpha 1-antitrypsin is an antiprotease found in human plasma that inhibits the neutrophil elastase enzyme from degrading elastin tissues in the lung. According to American Thoracic Society (2003) guidelines, a "protective" threshold plasma AAT level of 11 micromol/L corresponds to 80 mg/dl if measured by radial immunodiffusion and to 50 mg/dl if measured by nephelometry. This protective threshold has evolved from the observation that patients with heterozygote phenotypes whose levels of AAT exceed this level are usually free from emphysema.

VII. REFERENCES

1. Aralast NP [package insert]. Lexington, MA: Baxalta US Inc.; March 2023.
2. Glassia [package insert]. Lexington, MA: Takeda Pharmaceuticals US Inc.; September 2023.
3. Prolastin-C Liquid [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC.; May 2020.
4. Prolastin-C [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC.; January 2022.
5. Zemaira [package insert]. Kankakee, IL: CSL Behring LLC; September 2022.
6. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*. 2003;168:818-900.

7. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. *Can Respir J*. 2012;19:109-116.

AMONDYS 45 (casimersen)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Amondys 45 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Amondys 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 45 skipping (refer to examples in Appendix).
B. Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD).

IV. CRITERIA FOR INITIAL APPROVAL

Duchenne muscular dystrophy
Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:
A. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
B. The DMD gene mutation is amenable to exon 45 skipping (refer to examples in Appendix).
C. Treatment with Amondys 45 is initiated before the age of 14.
D. The member is able to achieve an average distance of at least 300 meters while walking independently over 6 minutes.
E. Dose will not exceed 30 mg/kg once weekly.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with Amondys 45.
B. Amondys 45 is being used to treat an indication enumerated in Section IV.
C. The member has demonstrated a response to therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent).
D. The member will not exceed a dose of 30 mg/kg once weekly.

VI. APPENDIX

Examples of DMD gene mutations (exon deletions) amenable to exon 45 skipping (not an all-inclusive list):

1. Deletion of exon 44
2. Deletion of exon 46-47
3. Deletion of exon 46-48
4. Deletion of exon 46-49
5. Deletion of exon 46-51
6. Deletion of exon 46-53
7. Deletion of exon 46-55

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Amondys 45.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Amondys 45 are covered.

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for requiring a minimum six-minute walk time of greater than 300 meters can be found in the inclusion criteria for the ESSENCE trial.

IX. REFERENCES

1. Amondys 45 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc; February 2021.
2. ClinicalTrials.gov. Study of SRP-4045 and SRP-4053 in DMD patients (ESSENCE). Available at: https://clinicaltrials.gov/ct2/show/NCT02500381. Accessed March 1, 2021.
3. Fletcher, S., et. al. Dystrophin Isoform Induction In Vivo by Antisense-mediated Alternative Splicing. The American Society of Gene & Cell Therapy. 2010;18(6):1218-1223.
4. Polavarapu K, Preethish-Kumar V, Sekar D, et al. Mutation pattern in 606 Duchenne muscular dystrophy children with a comparison between familial and non-familial forms: a study in an Indian large single-center cohort. J Neurol. 2019;266(9):2177-2185.

AMTAGVI (lifileucel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Amtagvi is indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Chart notes, medical record documentation or claims history supporting previous lines of therapy.

III. CRITERIA FOR INITIAL APPROVAL

Melanoma
Authorization of 3 months may be granted for treatment of unresectable or metastatic melanoma in members 18 years and older when all of the following criteria are met:
1. The member has received prior treatment with the following drug categories:
   i. PD-1 blocking antibody (e.g., Keytruda, Opdivo)
   ii. BRAF inhibitor (e.g., Braftovi, Tafinlar, Zelboraf) with or without a MEK inhibitor (e.g., Cotellic, Mekinist, Mektovi) if BRAF V600 mutation positive
2. The member has not received previous treatment with the requested medication.
3. The member does not have uveal or ocular melanoma.
4. The member does not have uncontrolled brain metastases.
5. The member has not had organ allograft (except kidney transplant) or prior cell transfer.
6. The member has adequate and stable kidney, pulmonary and cardiac function.
7. The member has an ECOG performance status of 0 or 1.
8. The member does not have clinically significant active infection.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Amtagvi.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Amtagvi [package insert]. Philadelphia, PA: Iovance Biotherapeutics Manufacturing LLC; February 2024.

AMVUTTRA (vutrisiran)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Amvuttra is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests: testing or analysis confirming a mutation of the TTR gene
B. For continuation requests: medical record documentation confirming the member demonstrates clinical benefit

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a neurologist, geneticist, or physician specializing in the treatment of amyloidosis.

IV. CRITERIA FOR INITIAL APPROVAL

Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis
Authorization of 12 months may be granted for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (also called transthyretin-type familial amyloid polyneuropathy [ATTR-FAP]) when all of the following criteria are met:
A. The diagnosis is confirmed by detection of a mutation of the TTR gene.
B. Member exhibits clinical manifestations of ATTR-FAP (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy).
C. The member is not a liver transplant recipient.
D. The requested medication will not be used in combination with inotersen (Tegsedi), patisiran (Onpattro) or tafamidis (Vyndaqel, Vyndamax).

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving treatment with Amvuttra
B. Amvuttra is being used for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis.
C. There is a clinical benefit from Amvuttra therapy.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Amvuttra.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Guideline of transthyretin-related hereditary amyloidosis for clinicians
4. Familial transthyretin amyloidosis. In: GeneReviews

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Amvuttra are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the above initial criteria can be found in a guideline from Ando and colleagues and a Gene Reviews chapter discussing hereditary transthyretin amyloidosis. The diagnosis of ATTR should be suspected in patients with progressive sensorimotor and/or autonomic neuropathy. The diagnosis of hereditary ATTR is established when characteristic clinical features are present, a biopsy showing amyloid deposits that bind to anti-TTR antibodies, and identification of mutations of the TTR gene.
The treatment for peripheral and autonomic neuropathy is orthotopic liver transplantation, TTR tetramer stabilizers and gene-silencing therapies (such as Amvuttra). Liver transplantation provides a wild type gene expressing normal TTR in the liver. Successful liver transplantation results in the disappearance of the variant TTR protein and thus halts the progression of peripheral and/or autonomic neuropathy.

VIII. REFERENCES

1. Amvuttra [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; June 2022.
2. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L, Planté-Bordeneuve V, Rapezzi C, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013; 8:31.
3. Sekijima Y, Yoshida K, Tokuda T, Ikeda S. Familial transthyretin amyloidosis. In: GeneReviews. Seattle (WA): University of Washington, Seattle. 1993-2017. https://www.ncbi.nlm.nih.gov/books/NBK1194/. Accessed March 16, 2023.

ANKTIVA (nogapendekin alfa inbakicept-pmln)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Anktiva is indicated with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Bladder Cancer
Authorization of 6 months may be granted for treatment of bladder cancer when all of the following criteria are met:
1. The member has non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors
2. The disease is Bacillus Calmette-Guerin (BCG)-unresponsive
3. The requested medication will be used in combination with Bacillus Calmette-Guerin (BCG)
4. The member will receive maintenance doses at months 4, 7, 10, 13 and 19 after induction therapy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months [for a total of 24 maintenance doses (37 months of treatment)] may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease recurrence or progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Anktiva.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs

*Please note: CMS may have policies (e.g. NCDs, LCDs) that preclude the Part B drug criteria contained in this document

*Please note: CMS may have policies (e.g. NCDs, LCDs) that preclude the Part B drug criteria contained in this document

e. Clinical Pharmacology

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Anktiva [package insert]. Bothell, WA: AGC Biologics; April 2024.

*Please note: CMS may have policies (e.g. NCDs, LCDs) that preclude the Part B drug criteria contained in this document

APHEXDA (motixafortide)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Aphexda is indicated in combination with filgrastim (G-CSF [granulocyte-colony stimulating factor]) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Hematopoietic Stem Cell Mobilization
Authorization of 6 months may be granted in members with multiple myeloma when all of the following criteria are met:
A. The requested medication will be used to mobilize hematopoietic stem cells for collection.
B. The requested medication will be administered after the member has received four daily doses of G-CSF (e.g., filgrastim).
C. The requested medication will not be used beyond two doses or after completion of stem cell harvest/apheresis.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent. Authorization for 6 months may be granted when all initial authorization criteria are met.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Aphexda.
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aphexda are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Aphexda [package insert]. Waltham, MA: BioLineRx USA Inc; September 2023.

ARANESP (darbepoetin alfa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Treatment of anemia due to:
1. Chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.
2. The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Limitations of Use:
1. Aranesp has not been shown to improve quality of life, fatigue, or patient well-being.
2. Aranesp is not indicated for use:
   - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
   - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
   - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
   - As a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

Note: Use in members on dialysis is covered under the Medicare Part B dialysis benefit and is excluded from coverage under this policy.

B. Compendial Uses
1. Treatment of anemia due to myelodysplastic syndrome
2. Prophylaxis of anemia of prematurity
3. Anemia in members whose religious beliefs forbid blood transfusions
4. Anemia in myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis
5. Cancer patients who are undergoing palliative treatment

C. Nationally Covered Indication
Centers for Medicare and Medicaid Services guidelines provide coverage for Aranesp for anemia secondary to myelosuppressive chemotherapy based on the criteria in Sections II, III, and IV.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

The following exclusions criteria apply to members requesting use for anemia due to concomitant myelosuppressive chemotherapy:
A. The anemia is due to folate, B-12, or iron deficiency.
B. The anemia is due to hemolysis, bleeding, or bone marrow fibrosis.
C. The anemia is due to treatment for acute myelogenous leukemia, chronic myelogenous leukemia, or erythroid cancers.
D. The anemia is due to cancer not related to cancer treatment.
E. The anemia is due to treatment with radiotherapy only.

F. Prophylactic use to prevent chemotherapy-induced anemia.
G. Prophylactic use to reduce tumor hypoxia.
H. Use in members with erythropoietin-type resistance due to neutralizing antibodies.
I. Members with uncontrolled hypertension.

III. CRITERIA FOR INITIAL APPROVAL

Note: Requirements regarding hemoglobin level exclude values due to a recent transfusion.

A. Anemia due to chronic kidney disease
Authorization of 12 weeks may be granted for the treatment of anemia due to chronic kidney disease in members not receiving dialysis with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

B. Anemia due to concomitant myelosuppressive chemotherapy
Authorization of 8 weeks may be granted for the treatment of anemia due to concomitant chemotherapy in members when all of the following criteria are met:
1. The member is receiving chemotherapy for a solid tumor, multiple myeloma, lymphoma, or lymphocytic leukemia.
2. The hemoglobin level immediately prior to initiation or maintenance of therapy is less than 10 g/dL or the hematocrit is less than 30%.
3. The starting dose is not greater than an average of 2.25 mcg/kg per week.

C. Anemia due to myelodysplastic syndrome
Authorization of 12 weeks may be granted for the treatment of anemia due to myelodysplastic syndrome in members with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

D. Prophylaxis of anemia of prematurity
Authorization of 12 weeks may be granted for the prophylaxis of anemia of prematurity in members less than 1 year of age.

E. Anemia in members whose religious beliefs forbid blood transfusions
Authorization of 12 weeks may be granted for treatment of anemia in members whose religious beliefs forbid blood transfusions whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

F. Anemia in myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis
Authorization of 12 weeks may be granted for the treatment of anemia due to myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis when all of the following criteria are met:
1. The member has a hemoglobin level less than 10 g/dL or hematocrit less than 30%.
2. The member has an erythropoietin (EPO) level of less than 500 mU/mL.

G. Anemia Due to Cancer
Authorization of 12 weeks may be granted for treatment of anemia in members who have cancer and are undergoing palliative treatment.

IV. CONTINUATION OF THERAPY

Note: Requirements regarding current hemoglobin level exclude values due to a recent transfusion.

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization of 12 weeks may be granted for treatment of anemia due to concomitant myelosuppressive chemotherapy when all of the following criteria are met:
1. The member is currently receiving therapy with Aranesp.
2. The member does not have any exclusions listed in Section II.

3. The member has experienced at least a 1 g/dL increase in their hemoglobin or a 3% increase in their hematocrit.
4. The member's hemoglobin remains below 11 g/dL or the prescriber will hold or reduce the dose of Aranesp to maintain a hemoglobin level sufficient to avoid transfusion.
5. Treatment will not extend beyond 8 weeks following the final dose of myelosuppressive chemotherapy given in the member's current chemotherapy regimen.

B. Authorization of 12 weeks may be granted for all other indications when all of the following criteria are met:
1. The member is currently receiving therapy with Aranesp.
2. The member is receiving Aranesp for an indication listed in Section III.
3. Aranesp has been effective for treating the diagnosis or condition.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Aranesp.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Anemia for Chronic Kidney Disease
4. Use of Epoetin and Darbepoetin in Patients with Cancer: American Society of Clinical Oncology (ASCO)/American Society of Hematology Clinical Practice Guideline Update
5. NCCN guideline: Myelodysplastic syndromes
6. NCCN guideline: Myeloproliferative neoplasms
7. NCCN guideline: Hematopoietic growth factors
8. Medicare National Coverage Determinations (NCD) Manual

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aranesp are covered in addition to the following:
A. Treatment of anemia due to myelodysplastic syndrome
B. Prophylaxis of anemia in prematurity
C. Anemia in members whose religious beliefs forbid blood transfusions
D. Anemia in myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis
E. Cancer patients who are undergoing palliative treatment

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications (anemia due to chronic kidney disease, anemia due to chemotherapy in members with cancer) can be found in the manufacturer's prescribing information.

Support for using darbepoetin alfa to treat anemia due to myelodysplastic syndrome can be found in the National Comprehensive Cancer Network's (NCCN) guideline for myelodysplastic syndromes. The NCCN Guideline for myelodysplastic syndrome supports the use of darbepoetin alfa for the treatment of symptomatic anemia associated with lower risk (IPSS low/intermediate-1) disease with del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7). Darbepoetin alfa can also be used for the treatment of symptomatic anemia associated with lower risk (IPSS-R very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an *SF3B1* mutation), with serum erythropoietin (EPO) ≤ 500 mU/mL as either a single agent, or in combination with either lenalidomide or granulocyte-colony stimulating factor (G-CSF) following no response or erythroid response followed by loss of response to an erythropoiesis-stimulating agent (ESA) alone. Finally, darbepoetin alfa can be used as treatment of symptomatic anemia associated with lower risk (IPSS-R very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring

sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an *SF3B1* mutation), with serum EPO ≤ 500 mU/mL as a single agent or in combination with a G-CSF.
In a single-arm study (N=206), treatment with darbepoetin alfa produced favorable erythroid responses in patients with anemia due to low-risk myelodysplastic syndromes. At week 13 and over the course of the study, 17% and 28% of ESA-naive patients and 35% and 42% of prior ESA-treated patients required a red blood cell (RBC) transfusion. A major and minor erythroid response rate occurred in 49% and 22% of ESA-naive patients and in 26% and 18% in ESA-experienced patients at week 13, and at the end of the study at 53 or 55 weeks the major and minor response rates were 59% and 15% of ESA-naive patients and 34% and 16% in ESA-experienced patients (Gabrilove et al., (2008)).
The American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) Clinical Practice Guidelines titled "Use of Epoetin and Darbepoetin in Patients With Cancer" (2007) state that some evidence supports the use of darbepoetin alfa in patients with anemia associated with low-risk myelodysplasia.

Support for using darbepoetin alfa for prophylaxis against anemia of prematurity can be found in a study by Ohls et al. (2013). Erythropoiesis-stimulating agents (ESA; darbepoetin alfa and erythropoietin) reduced the need for blood transfusions compared with placebo in preterm infants (mean birth weight, 946 g; mean gestation, 27.7 weeks) at 4 high-altitude institutions using a restrictive transfusion protocol in a randomized trial (n=102). Infants received either darbepoetin 10 mcg/kg subcutaneously (subQ) once weekly, erythropoietin 400 units/kg subQ 3 times weekly, or placebo until the completion of 35 weeks' gestation. The mean number of transfusions/subjects was lower in the ESA groups compared with the placebo group (1.2 in both darbepoetin alfa and erythropoietin vs 2.4 in placebo). However, there was no significant difference in the number of transfusion-free patients in the ESA groups when compared with placebo. Absolute reticulocyte count and hematocrit were significantly higher and donor exposure was lower in the ESA groups compared with the placebo group. There was no difference between the ESA and placebo groups in mortality and preterm morbidity.

Support for using darbepoetin alfa to treat anemia in patients whose religious beliefs forbid blood transfusions can be found in a review article by Lawson and Ralph (2015). Recombinant erythropoietin is the most frequently used erythropoiesis-stimulating agent (ESA). It was first used in the treatment of anemia secondary to end-stage renal disease. Recombinant erythropoietin acts by stimulating the following: (i) proliferation and differentiation of erythroid precursors to increase immature erythrocyte production; (ii) release of erythrocytes from bone marrow; and (iii) hemoglobin (Hb) production. It may also protect cells by inhibiting various protein kinase cascades while increasing stem cell recruitment into damaged areas and has platelet-activating effects. The effects of recombinant erythropoietins are partly governed by ferritin, transferrin, iron, vitamin B12, and folic acid concentrations. Before surgery, it is important to check which recombinant erythropoietin preparation is being used because some do contain trace amounts of human albumin, which may conflict with the beliefs of some Jehovah's Witnesses. The response appears to be dose dependent, with an increase in reticulocyte count being seen within 10 days and new erythropoiesis within 1–6 weeks.
Four Jehovah's Witness patients who either exhibited preoperative anemia or developed postoperative anemia refractory to endogenous erythropoietin were discharged from the hospital in good condition after treatment with recombinant human erythropoietin (EPO) 50 to 280 Units per kilogram body weight daily. The fifth patient, who exhibited no signs of systemic inflammation following emergency hemicolectomy, was also treated with intravenous iron, but not with erythropoietin. No predictor of response was identified in this series; therefore, use of erythropoietin in this patient subgroup would be based strictly on humanitarian grounds (Wolff et al., 1997).

Support for using darbepoetin alfa to treat myelofibrosis-associated anemia can be found in the National Comprehensive Cancer Network's guideline for myeloproliferative neoplasms. The NCCN Guideline supports the use darbepoetin alfa for the management of myelofibrosis-associated anemia with serum erythropoietin less than 500 mU/mL.

Support for using darbepoetin alfa to treat anemia in patients who have cancer and are undergoing palliative treatment can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors.

Use in cancer and related neoplastic conditions is covered according to the conditions outlined in the National Coverage Determination Manual section 110.21 (Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions).

VII. REFERENCES

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ARRANON (nelarabine)
nelarabine

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Arranon is indicated for the treatment of T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in adult and pediatric patients age 1 year and older whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. T-cell Acute Lymphoblastic Leukemia (T-ALL)
Authorization of 6 months may be granted for the treatment of T-cell ALL when the patient is at least one year of age and whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.

B. T-cell Lymphoblastic Lymphoma (T-LBL)
Authorization of 6 months may be granted for the treatment of T-cell lymphoblastic lymphoma when the patient is at least one year of age and whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy (e.g. disease stabilization or improvement)
D. The member has no evidence of unacceptable toxicity while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for nelarabine.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Acute Lymphoblastic Leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for nelarabine are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using nelarabine to treat T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in adult and pediatric patients age 1 year and older can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

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ASPARLAS (calaspargase pegol-mknl)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Asparlas is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years.

B. Compendial Uses
1. Lymphoblastic lymphoma (managed in the same manner as ALL)
2. Acute lymphoblastic leukemia (ALL) as a substitute for pegaspargase in patients 21 years and younger for more sustained asparaginase activity
3. Pediatric acute lymphoblastic leukemia (ALL) as a substitute for pegaspargase in patients age 1 month to 21 years for more sustained asparaginase activity

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Acute lymphoblastic leukemia/lymphoma
Authorization of 12 months may be granted for treatment of acute lymphoblastic leukemia or lymphoblastic lymphoma when all of the following criteria are met:
A. The requested medication will be used in conjunction with multi-agent chemotherapy
B. The member is 21 years of age or younger

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Asparlas.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. NCCN Guideline: Acute lymphoblastic leukemia
4. NCCN Guideline: Pediatric lymphoblastic leukemia
5. Lymphoblastic Lymphoma: Guidelines From the International Radiation Oncology Group (ILROG).

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Asparlas are covered in addition to the following:

1. Lymphoblastic lymphoma (managed in the same manner as ALL)
2. Acute lymphoblastic leukemia (ALL) as a substitute for pegaspargase in patients 21 years and younger for more sustained asparaginase activity
3. Pediatric acute lymphoblastic leukemia (ALL) as a substitute for pegaspargase in patients age 1 month to 21 years for more sustained asparaginase activity

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Asparlas to treat lymphoblastic lymphoma and acute lymphoblastic leukemia (used as a substitute for pegaspargase) can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

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AVASTIN (bevacizumab) – Oncology
ALYMSYS (bevacizumab-maly) – Oncology
MVASI (bevacizumab-awwb) – Oncology
VEGZELMA (bevacizumab-adcd) - Oncology
ZIRABEV (bevacizumab-bvzr) – Oncology

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Metastatic colorectal cancer (mCRC)
   i. Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer.
   ii. Avastin/Alymsys/Mvasi/Vegzelma/Zirabev in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen.
2. First-line non-squamous non-small cell lung cancer (NSCLC)
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer.
3. Recurrent glioblastoma (GBM)
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev is indicated for the treatment of recurrent glioblastoma in adults.
4. Metastatic renal cell carcinoma (mRCC)
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma.
5. Persistent, recurrent, or metastatic cervical cancer
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.
6. Epithelial ovarian, fallopian tube, or primary peritoneal cancer
   i. Avastin/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, followed by Avastin/Mvasi/Vegzelma/Zirabev as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.
   ii. Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.
   iii. Avastin/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin/Mvasi/Vegzelma/Zirabev as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
7. Hepatocellular carcinoma
   Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

B. Compendial Uses
1. Advanced gastric cancer
2. Advanced liver carcinoma

3. Breast cancer
4. Central nervous system (CNS) cancers
    i. Glioma (WHO Grade 1)
    ii. Diffuse high grade gliomas
    iii. Glioblastoma
    iv. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
    v. Oligodendroglioma (WHO Grade 2 or 3)
    vi. Intracranial and spinal ependymoma (excludes subependymoma)
    vii. Medulloblastoma
    viii. Primary central nervous system lymphoma
    ix. Meningiomas
    x. Limited and extensive brain metastases
    xi. Metastatic spine tumors
5. Necrosis of central nervous system due to exposure to ionizing radiation
6. Malignant pleural mesothelioma, Malignant peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
7. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
8. Soft tissue sarcoma
    i. Angiosarcoma
    ii. Solitary fibrous tumor/Hemangiopericytoma
9. Uterine neoplasms/Endometrial carcinoma
10. Vulvar carcinoma
11. Small bowel adenocarcinoma
12. Ampullary adenocarcinoma
13. Appendiceal adenocarcinoma
14. Anal adenocarcinoma
15. Renal cell carcinoma

C. Nationally Covered Indications
CMS covers bevacizumab for use in specific clinical trials (NCI-CMS Pilot Project). Refer to the Appendix for a list of these covered clinical trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

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II. CRITERIA FOR INITIAL APPROVAL

A. Colorectal cancer
Authorization of 12 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma.

B. Non-small cell lung cancer
Authorization of 12 months may be granted for treatment of symptomatic local, recurrent, unresectable, advanced or metastatic non-squamous non-small cell lung cancer.

C. Renal cell cancer
Authorization of 12 months may be granted for treatment of relapsed or stage IV renal cell cancer.

D. Cervical/Vaginal cancer
Authorization of 12 months may be granted for treatment of persistent, recurrent, or metastatic cervical or vaginal cancer.

E. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
Authorization of 12 months may be granted for treatment of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and malignant sex cord stromal tumors.

F. Hepatocellular carcinoma

Authorization of 12 months may be granted for treatment of unresectable or metastatic hepatocellular carcinoma, when the requested medication will be used as initial treatment in combination with atezolizumab.

G. Gastric cancer
Authorization of 12 months may be granted for treatment of gastric cancer.

H. Liver cancer
Authorization of 12 months may be granted for treatment of liver cancer.

I. Central nervous system (CNS) cancer
Authorization of 12 months may be granted for treatment of the following types of CNS cancer:
1. Glioma (WHO Grade 1)
2. Diffuse high grade gliomas
3. Glioblastoma
4. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
5. Oligodendroglioma (WHO Grade 2 or 3)
6. Intracranial and spinal ependymoma (excluding subependymoma)
7. Medulloblastoma
8. Primary central nervous system lymphoma
9. Meningiomas
10. Limited and extensive brain metastases
11. Metastatic spine tumors

J. Necrosis of central nervous system due to exposure to ionizing radiation
Authorization of 3 months may be granted for treatment of central nervous system necrosis due to exposure to ionizing radiation.

K. Uterine neoplasms/Endometrial carcinoma
Authorization of 12 months may be granted for treatment of progressive, advanced, recurrent, or metastatic uterine neoplasms or endometrial carcinoma.

L. Mesothelioma
1. Authorization of 12 months may be granted for treatment of malignant pleural mesothelioma, malignant peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when any of the following criteria are met:
    i. As first-line therapy for unresectable disease in combination with pemetrexed and either cisplatin or carboplatin, followed by single-agent maintenance bevacizumab
    ii. As subsequent therapy in combination with pemetrexed and either cisplatin or carboplatin if immunotherapy was administered as first-line treatment
2. Authorization of 12 months may be granted for treatment of malignant peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when used in combination with atezolizumab as subsequent therapy.

M. Breast cancer
Authorization of 12 months may be granted for treatment of recurrent or metastatic breast cancer.

N. Soft tissue sarcoma
1. Authorization of 12 months may be granted for treatment of angiosarcoma, as single agent therapy.
2. Authorization of 12 months may be granted for treatment of solitary fibrous tumor or hemangiopericytoma, in combination with temozolomide.

O. Vulvar carcinoma
Authorization of 12 months may be granted for treatment of unresectable locally advanced, recurrent, or metastatic vulvar carcinoma, including squamous cell carcinoma and adenocarcinoma.

P. Small bowel adenocarcinoma
Authorization of 12 months may be granted for treatment of small bowel adenocarcinoma.

Q. Ampullary adenocarcinoma
Authorization of 12 months may be granted for treatment of intestinal-type ampullary adenocarcinoma that is progressive, unresectable, or metastatic.

R. NCD indications
Authorization of 12 months may be granted for treatment of patients enrolled in any of the studies listed in the Appendix section.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization for 3 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat central nervous system necrosis due to exposure to ionizing radiation.
   3. The member is receiving benefit from therapy.

B. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat an indication enumerated in Section II (excluding central nervous system necrosis due to exposure to ionizing radiation).
   3. The member is receiving benefit from therapy. Benefit is defined as:
      i. No evidence of unacceptable toxicity while on the current regimen and
      ii. No evidence of disease progression while on the current regimen.

IV. APPENDIX

NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project (Studies in Various Stages of Development)

Study ID #	Study Title
C80405	Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab, or with the combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum
E2204	An Intergroup Randomized Phase II Study of Bevacizumab or Cetuximab in Combination with Gemcitabine and in Combination with Chemoradiation (Capecitabine and Radiation) in Patients with Completely-Resected Pancreatic Carcinoma
E4203	Phase II Study of Treatment Selection Based Upon Tumor Thymidylate Synthase Expression in Previously Untreated Patients with Metastatic Colorectal Cancer
E5202	Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers
E5204	Intergroup Randomized Phase III Study of Post-Operative Oxaliplatin, 5-Fluorouracil and Leucovorin with or without Bevacizumab in Patients with Stage II or III Rectal Cancer Receiving Pre-Operative Radiation and a 5-Fluorouracil-Based Regimen

NSABP-R-04	A Clinical Trial Comparing Preoperative Radiation Therapy and Capecitabine with or without Oxaliplatin with Preoperative Radiation Therapy and Continuous Intravenous Infusion 5-Fluorouracil with or without Oxaliplatin in the Treatment of Patients with Operable Carcinoma of the Rectum
RTOG-0522	Phase III Trial of Concurrent Accelerated Radiation & Cisplatin vs Concurrent Accelerated Radiation, Cisplatin, & Cetuximab (Followed by Surgery for Selected Patients) for Stage III & IV Head & Neck Carcinomas
S0502	Phase III Randomized Study of Imatinib, with or without Bevacizumab, in Patients with Metastatic or Unresectable Gastrointestinal Stromal Tumors
7325	Dose-Dense and Dose-Intense Alternating Irinotecan/Capecitabine & Oxaliplatin/Capecitabine: Phase I in Solid Tumors and Phase II with Bevacizumab as First-Line Therapy of Advanced Colorectal Cancer

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Avastin, Alymsys, Mvasi, Vegzelma, and Zirabev.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Vulvar cancer
4. NCCN Guideline: Cervical cancer
5. NCCN Guideline: Small bowel adenocarcinoma
6. NCCN Guideline: Peritoneal mesothelioma
7. NCCN Guideline: Pleural mesothelioma
8. NCCN Guideline: Non-small cell lung cancer
9. NCCN Guideline: Hepatocellular carcinoma
10. NCCN Guideline: Central nervous system cancers
11. NCCN Guideline: Ampullary adenocarcinoma
12. NCCN Guideline: Ovarian cancer, including fallopian tube cancer and primary peritoneal cancer
13. NCCN Guideline: Kidney cancer
14. NCCN Guideline: Uterine neoplasms
15. NCCN Guideline: Soft tissue sarcoma
16. NCCN Guideline: Colon cancer
17. NCCN Guideline: Rectal cancer
18. National Coverage Determination (NCD) for Anti-cancer Chemotherapy for Colorectal Cancer (110.17)
19. NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Avastin, Alymsys, Mvasi, Vegzelma, and Zirabev are covered in addition to the following:

1. Inclusion in NCI/CTEP-sponsored studies selected for inclusion in NCI-CMS pilot project
2. Advanced gastric cancer
3. Advanced liver carcinoma
4. Breast cancer
5. Central nervous system (CNS) cancers
    i. Glioma (WHO Grade 1)
    ii. Diffuse high grade gliomas
    iii. Glioblastoma
    iv. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
    v. Oligodendroglioma (WHO Grade 2 or 3)

vi. Intracranial and spinal ependymoma (excludes subependymoma)
vii. Medulloblastoma
viii. Primary central nervous system lymphoma
ix. Meningiomas
x. Limited and extensive brain metastases
xi. Metastatic spine tumors
6. Necrosis of central nervous system due to exposure to ionizing radiation
7. Malignant pleural mesothelioma, Malignant peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
8. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
9. Soft tissue sarcoma
   i. Angiosarcoma
   ii. Solitary fibrous tumor/Hemangiopericytoma
10. Uterine neoplasms/Endometrial carcinoma
11. Vulvar carcinoma
12. Small bowel adenocarcinoma
13. Ampullary adenocarcinoma
14. Appendiceal adenocarcinoma
15. Anal adenocarcinoma
16. Renal cell carcinoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using bevacizumab for the below listed indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

1. Central nervous system (CNS) cancers
   i. Glioma (WHO Grade 1)
   ii. Diffuse high grade gliomas
   iii. Glioblastoma
   iv. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
   v. Oligodendroglioma (WHO Grade 2 or 3)
   vi. Intracranial and spinal ependymoma (excludes subependymoma)
   vii. Medulloblastoma
   viii. Primary central nervous system lymphoma
   ix. Meningiomas
   x. Limited and extensive brain metastases
   xi. Metastatic spine tumors
2. Necrosis of central nervous system due to exposure to ionizing radiation
3. Malignant pleural mesothelioma, Malignant peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
4. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
5. Soft tissue sarcoma
   i. Angiosarcoma
   ii. Solitary fibrous tumor/Hemangiopericytoma
6. Uterine neoplasms/Endometrial carcinoma
7. Vulvar carcinoma
8. Small bowel adenocarcinoma
9. Ampullary adenocarcinoma
10. Appendiceal adenocarcinoma
11. Anal adenocarcinoma
12. Renal cell carcinoma

Support for using bevacizumab for advanced gastric cancer, advanced liver carcinoma and breast cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use

of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Use of bevacizumab in an NCI/CTE-sponsored study is covered according to the conditions outlined in National Coverage Determination Manual section 110.17 Anti-Cancer Chemotherapy for Colorectal Cancer.

VII. REFERENCES

1. Avastin [package insert]. South San Francisco, CA: Genentech, Inc.; September 2022.
2. Alymsys [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; April 2022.
3. Mvasi [package insert]. Thousand Oaks, CA: Amgen Inc.; November 2021.
4. Zirabev [package insert]. New York, NY: Pfizer Inc.; May 2021.
5. Vegzelma [package insert]. Incheon, Republic of Korea: Celltrion, Inc.; September 2022.
6. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed November 15, 2022.
7. Micromedex Solutions [database online]. Truven Health Analytics, Greenwood Village, CO. Available at: https://www.micromedexsolutions.com. Accessed November 16, 2022.
8. National Coverage Determination (NCD) for Anti-cancer Chemotherapy for Colorectal Cancer (110.17) Version 1. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=291&ncdver=1&kc=dc634fd6-c&bc=AAAAAAgAAAAAAA%3d%3d&. Accessed November 22, 2022.
9. NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project. https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id90b.pdf. Accessed November 22, 2022.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 22, 2022.
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed November 22, 2022.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf. Accessed November 22, 2022.
13. Lexicomp [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/home [available with subscription]. Accessed November 22, 2022.

BAVENCIO (avelumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Metastatic Merkel Cell Carcinoma (MCC)
   Treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma
2. Locally Advanced or Metastatic Urothelial Carcinoma (UC)
   i. Maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy
   ii. Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
3. Advanced Renal Cell Carcinoma (RCC)
   First-line treatment of patients with advanced renal cell carcinoma in combination with axitinib

B. Compendial Uses
1. Urothelial carcinoma
   i. Bladder cancer
   ii. Primary carcinoma of the urethra
   iii. Upper genitourinary (GU) tract tumor
   iv. Urothelial carcinoma of the prostate
2. Merkel cell carcinoma
3. Renal cell carcinoma
4. Gestational trophoblastic neoplasia
5. Endometrial carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Merkel Cell Carcinoma
Authorization of 12 months may be granted for the treatment of Merkel cell carcinoma in members with metastatic disease.

B. Urothelial Carcinoma – Bladder Cancer
Authorization of 12 months may be granted for the treatment of bladder cancer as a single agent when either of the following criteria is met:
1. The requested drug will be used as maintenance therapy if there is no progression on first-line platinum-containing chemotherapy.
2. The requested drug will be used as subsequent therapy in any of the following settings:
   i. Disease is locally advanced or metastatic
   ii. Member has muscle invasive local recurrence or persistent disease in a preserved bladder
   iii. Member has metastatic or local recurrence post-cystectomy
   iv. Member has Stage II or IIIA disease and tumor is present following primary treatment

C. Urothelial Carcinoma – Primary Carcinoma of the Urethra

Authorization of 12 months may be granted for the treatment of primary carcinoma of the urethra as a single agent when either of the following criteria is met:

1. The requested drug will be used as maintenance therapy if there is no progression on first-line platinum-containing chemotherapy.
2. The requested drug will be used as subsequent systemic therapy for recurrent, locally advanced, or metastatic disease.

D. Urothelial Carcinoma – Upper Genitourinary (GU) Tract Tumors or Urothelial Carcinoma of the Prostate

Authorization of 12 months may be granted for the treatment of upper genitourinary (GU) tract tumors or urothelial carcinoma of the prostate as a single agent when either of the following criteria is met:

1. The requested drug will be used as maintenance therapy if there is no progression on first-line platinum-containing chemotherapy.
2. The requested drug will be used as subsequent therapy for locally advanced or metastatic disease

E. Renal cell carcinoma

Authorization of 12 months may be granted for the treatment of advanced, relapsed, or stage IV renal cell carcinoma when Bavencio is given in combination with axitinib as first-line treatment for the disease.

F. Gestational trophoblastic Neoplasia

Authorization of 12 months may be granted for the treatment of gestational trophoblastic neoplasia as a single agent for multiagent chemotherapy-resistant disease when either of the following criteria is met:

1. Member has recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor) following treatment with a platinum-based regimen
2. Member has high-risk disease

G. Endometrial Carcinoma

Authorization of 12 months may be granted as a single agent for second-line treatment of recurrent or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with Bavencio.
B. Bavencio is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen and
    ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Bavencio.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Gestational trophoblastic neoplasia
4. NCCN Guideline: Merkel cell carcinoma
5. NCCN Guideline: Kidney cancer
6. NCCN Guideline: Bladder cancer
7. NCCN Guideline: Uterine neoplasms

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Bavencio are covered in addition to the following:

1. Urothelial carcinoma
    i. Bladder cancer
    ii. Primary carcinoma of the urethra
    iii. Upper genitourinary (GU) tract tumor
    iv. Urothelial carcinoma of the prostate
2. Merkel cell carcinoma
3. Renal cell carcinoma
4. Gestational trophoblastic neoplasia
5. Endometrial carcinoma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for urothelial carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for Merkel cell carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for renal cell carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for gestational trophoblastic neoplasia can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for endometrial carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Bavencio [package insert]. Rockland, MA: EMD Serono, Inc.; November 2020.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 5, 2022.

BELEODAQ (belinostat)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)

B. Compendial Uses
T-Cell Lymphomas
1. Hepatosplenic T-cell lymphoma
2. Extranodal NK/T-cell lymphoma
3. Adult T-cell leukemia/lymphoma (ATLL)
4. Breast implant associated anaplastic large cell lymphoma (ALCL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

T-Cell Lymphomas
Authorization of 12 months may be granted for treatment T-cell lymphomas with any of the following subtypes:
1. Peripheral T-cell lymphoma [including the following subtypes: anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma] when both of the following criteria are met:
   i. The requested drug will be used as a single agent, and
   ii. The requested drug is used for relapsed or refractory disease or for palliative intent.
2. Hepatosplenic T-cell lymphoma when both of the following are met:
   i. The member has had two or more previous lines of chemotherapy, and
   ii. The requested drug will be used a single agent.
3. Extranodal NK/T-cell lymphoma when all of the following criteria are met:
   i. The requested drug will be used as a single agent, and
   ii. The member has relapsed or refractory disease, and
   iii. The member has had an inadequate response or contraindication to asparaginase-based therapy (e.g., pegaspargase).
4. Adult T-cell leukemia/lymphoma (ATLL) when both of the following criteria are met:
   i. The requested drug is used as a single agent, and
   ii. The requested drug is used for subsequent therapy.
5. Breast implant-associated anaplastic large cell lymphoma (ALCL) when both of the following criteria are met:

i. The requested drug is used as a single agent, and
ii. The requested drug is used for subsequent therapy

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested drug
2. The requested drug is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No unacceptable toxicity while on the current regimen AND
    ii. No disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Beleodaq.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guidelines: T-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Beleodaq are covered in addition to the following:
1. Hepatosplenic T-cell lymphoma
2. Extranodal NK/T-cell lymphoma
3. Adult T-cell leukemia/lymphoma (ATLL)
4. Breast implant associated anaplastic large cell lymphoma (ALCL)

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Beleodaq to treat hepatosplenic T-cell lymphoma, extranodal NK/T-cell lymphoma, adult T-cell leukemia/lymphoma, and breast implant-associated anaplastic large cell lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Beleodaq [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; April 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 5, 2023.

BENLYSTA (belimumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Benlysta is indicated for the treatment of:
A. Patients aged 5 years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy, and
B. Patients aged 5 years and older with active lupus nephritis who are receiving standard therapy.

Limitations of use
The efficacy of Benlysta has not been evaluated in patients with severe active central nervous system (CNS) lupus. Use of Benlysta is not recommended in this situation.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: Medical records (e.g., chart notes, lab reports) documenting the presence of autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins), or kidney biopsy supporting diagnosis (where applicable).
B. Continuation requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Severe active central nervous system (CNS) lupus (including seizures that are attributed to CNS lupus, psychosis, organic brain syndrome, cerebritis, or CNS vasculitis requiring therapeutic intervention within 60 days before initiation of belimumab) in a member initiating therapy with Benlysta.
B. Member is using Benlysta in combination with other biologics.

IV. CRITERIA FOR INITIAL APPROVAL

A. Systemic lupus erythematosus (SLE)
Authorization of 12 months may be granted for treatment of active SLE when all of the following criteria are met:
1. Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins)
2. The member meets either of the following criteria:
   i. The member is receiving a stable standard treatment for SLE with any of the following (alone or in combination):
      a. Glucocorticoids (e.g., prednisone, methylprednisolone, dexamethasone)
      b. Antimalarials (e.g., hydroxychloroquine)

c. Immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate, cyclosporine, cyclophosphamide)
d. Nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen, naproxen)

ii. The member has a clinical reason to avoid treatment with a standard treatment regimen.

B. Lupus nephritis

Authorization of 12 months may be granted for treatment of active lupus nephritis when all of the following criteria are met:

1. Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins) or lupus nephritis was confirmed on kidney biopsy.
2. Member is receiving a stable standard therapy regimen (e.g., cyclophosphamide, mycophenolate mofetil, azathioprine, corticosteroids) or has a clinical reason to avoid treatment with a standard therapy regimen.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section IV.
C. The member is receiving benefit from therapy. Benefit is defined as disease stability or improvement.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Benlysta.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus
4. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus
5. Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases
6. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus
7. Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Benlysta are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The content of the exclusions can be found in the prescribing information.

The British Society for Rheumatology report that ANAs are present in about 95% of SLE patients. If the test for ANAs is negative, there is a low clinical probability of a member having SLE. The presence of anti-dsDNA antibodies, low complement levels or anti-Smith (Sm) antibodies are highly predictive of a diagnosis of SLE in

patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE as they are found in other autoimmune rheumatic disorders as well as SLE.

The SLICC group devised alternative classification criteria for lupus. These criteria introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items compared with the ACR criteria. They also allowed biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA antibodies to be classified as lupus, without the need for other criteria.

THE EULAR/ACR classification criteria for SLE also requires ANA antibodies for the diagnosis of SLE. The diagnosis can be confirmed with a positive ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended.

According to the 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus, the goal of treatment should be remission or low disease activity and prevention of flares in all organs. Glucocorticoids can be used at doses and route of administration that depend on the type and severity of organ involvement. In patients not responding to hydroxychloroquine (alone or in combination with GC) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as methotrexate, azathioprine or mycophenolate should be considered. Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as 'rescue' therapy in patients not responding to other immunosuppressive agents. In patients with inadequate response to standard-of-care (combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with belimumab should be considered.

The British Society for Rheumatology indicates that SLE can be managed with corticosteroids, hydroxychloroquine and other antimalarials, methotrexate, and non-steroidal antiinflammatory drugs (NSAIDs). Patients who present with severe SLE, including renal and NP manifestations, need thorough investigation to exclude other etiologies, including infection. Treatment is dependent on the underlying etiology (inflammatory and/or thrombotic), and patients should be treated accordingly with immunosuppression and/or anticoagulation, respectively. Immunosuppressive regimens for severe active SLE involve intravenous methylprednisolone or high-dose oral prednisolone (up to 1 mg/kg/day) to induce remission, either on their own or more often as part of a treatment protocol with another immunosuppressive drug. Mycophenolate mofetil or cyclosporine are used for most cases of lupus nephritis and for refractory, severe non-renal disease. Biologic therapies belimumab or rituximab may be considered, on a case-by-case basis, where patients have failed to respond to other immunosuppressive drugs, due to inefficacy or intolerance.

VIII. REFERENCES

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2. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. *Ann Rheum Dis*. 2019;78:736-745.
3. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78:1151-1159.
4. Rovin BH, Adler SG, Barratt J, et al. Kidney Disease: Improving Global Outcomes (KDIGO) Golmerular Disease Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021 Oct; 100(4S):S1-S276.
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BEOVU (brolucizumab-dbll)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
1. Neovascular (wet) age-related macular degeneration
2. Diabetic macular edema

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Neovascular (wet) age-related macular degeneration
Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

Diabetic macular edema
Authorization of 12 months may be granted for treatment of diabetic macular edema

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when ALL of the following criteria are met:
A. The member is currently receiving therapy with Beovu.
B. Beovu is being used to treat an indication enumerated in Section II.
C. The medication has been effective for treating the diagnosis or condition.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Beovu.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Beovu are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Beovu [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2022.
2. Dugel PU, Koh A, Ogura Y et al. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2020; 127:72-84.

BEQVEZ (fidanacogene elaparvovec-dzkt)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Beqvez is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with moderate to severe Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes, and,
- Do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Chart notes, lab tests documenting all of the following (where applicable):

A. Severe to moderately severe Factor IX deficiency (≤2% of normal circulating Factor IX)
B. Absence of Factor IX inhibitors (lab test results required)
C. Current use of Factor IX prophylaxis therapy
D. History of life-threatening hemorrhage(s) or repeated, serious spontaneous bleeding episodes
E. Negative adeno-associated virus serotype Rh74var (AAVRh74var) antibody test result

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a hematologist.

IV. CRITERIA FOR INITIAL APPROVAL

Hemophilia B
Authorization of 1 month for one dose total may be granted for the treatment of hemophilia B when all of the following criteria are met:

A. Member is 18 years of age or older
B. Member meets either of the following:
    1. Member has a negative Factor IX inhibitor test result within the past 30 days
    2. If member has a positive Factor IX inhibitor test result within the past 30 days, there must be a negative test result within 2 weeks of the initial positive result
C. Member has severe or moderately severe Factor IX deficiency (≤2% of normal circulating Factor IX) and meets any of the following:
    1. Member is currently using Factor IX prophylactic therapy
    2. Member has a current or history of a life-threatening hemorrhage
    3. Member has a history of repeated, serious spontaneous bleeding episodes

D. Member has a negative adeno-associated virus serotype Rh74var (AAVRh74var) antibody test result
E. Member has not previously received gene therapy treatment

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Beqvez.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Beqvez are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Beqvez [package insert]. New York, NY: Pfizer Inc.; April 2024.

*Please note: CMS may have policies (e.g. NCDs, LCDs) that preclude the Part B drug criteria contained in this document

BERINERT (C1 esterase inhibitor [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Berinert is indicated for the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients.

B. Compendial Use
Short term preprocedural prophylaxis for HAE attacks

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial authorization:
   1. C1 inhibitor functional and antigenic protein levels
   2. F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
   3. Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
B. For continuation of therapy for acute attacks, chart notes demonstrating a reduction in severity and/or duration of attacks

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

IV. CRITERIA FOR INITIAL APPROVAL

Hereditary angioedema (HAE)

A. Preprocedural Prophylaxis
Authorization of 30 days may be granted for short-term preprocedural prophylaxis (i.e., prior to surgical or major dental procedures) when either of the following criteria is met at the time of diagnosis:
   1. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
      i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
      ii. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).

2. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    i. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    ii. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

B. Acute Attacks

Authorization of 6 months may be granted for treatment of acute HAE attacks when either of the following criteria is met at the time of diagnosis:

1. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
    ii. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
2. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    i. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    ii. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Preprocedural Prophylaxis

All members (including new members) requesting authorization for continued short-term preprocedural prophylaxis (i.e., prior to surgical or major dental procedures) must meet all initial authorization criteria.

B. Acute Attacks

Authorization of 12 months may be granted for continued treatment of acute HAE attacks when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy. Benefit is defined as reduction in severity and/or duration of acute attacks.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Berinert.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.

4. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
5. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
6. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.
7. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
8. International consensus on hereditary and acquired angioedema.
9. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.
10. Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.
11. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency.
12. Diagnosis and screening of patients with hereditary angioedema in primary care.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Berinert are covered in addition to short-term preprocedural prophylaxis for HAE attacks.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.
When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

Support for using Berinert as short term preprocedural prophylaxis against HAE attacks can be found in the US HAEA guidelines. The goal of preprocedural prophylaxis is to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to trigger an HAE attack. Acceptable short-term prophylaxis can be either Berinert or a course of anabolic androgen.

VIII. REFERENCES

1. Berinert [package insert]. Kankakee, IL: CSL Behring LLC; September 2021.
2. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010;6(1):24.
3. Cicardi M, Bork K, Caballero T, et al. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy.* 2012;67:147-157.
4. Kreuz W, Martinez-Saguer I, Aygoren-Pursun E. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion.* 2009;49:1987-1995.
5. Busse PJ, Christiansen, SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol: In Practice.* 2021 Jan;9(1):132-150.e3.
6. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc*. 2012; 33(6):S145-S156.

7. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update. *Allergy*. 2022 Jan 10. doi: 10.1111/all. 15214. Online ahead of print..
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9. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69: 602-616.
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13. Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. *Allergy*. 2017;72(2):300-313.
14. Henao MP, Kraschnewski J, Kelbel T, Craig T. Diagnosis and screening of patients with hereditary angioedema in primary care. *Therapeutics and Clin Risk Management.* 2016; 12: 701-711.
15. Veronez CL, Csuka D, Sheik FR, et al. The expanding spectrum of mutations in hereditary angioedema. *J Allergy Clin Immunol Pract.* 2021;S2213-2198(21)00312-3.

BESPONSA (inotuzumab ozogamicin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Besponsa is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

B. Compendial Use
Pediatric acute lymphoblastic leukemia (ALL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Testing or analysis confirming CD22 protein on the surface of the B-cell.

III. CRITERIA FOR INITIAL APPROVAL

Acute lymphoblastic leukemia (ALL)

A. Authorization of 12 months may be granted for treatment of ALL as induction therapy when all of the following criteria are met:
   1. Member has B-cell precursor ALL
   2. The tumor is CD22-positive as confirmed by testing or analysis to identify the CD22 protein on the surface of the B-cell
   3. Member has Philadelphia chromosome-negative disease
   4. Member is at least 65 years old or has substantial comorbidities
   5. The requested drug will be used in combination with cyclophosphamide, dexamethasone, vincristine, methotrexate and cytarabine
   6. Member will not receive more than 6 treatment cycles of the requested drug

B. Authorization of 12 months may be granted for treatment of relapsed or refractory ALL when all of the following criteria are met:
   1. Member has B-cell precursor ALL.
   2. The tumor is CD22-positive as confirmed by testing or analysis to identify the CD22 protein on the surface of the B-cell.
   3. Member meets one of the following:
      i. Member has Philadelphia chromosome-positive disease
      ii. Member has Philadelphia chromosome-negative disease
   4. The requested drug will be used in one of the following settings:
      i. As a single agent
      ii. In combination with a tyrosine kinase inhibitor for Philadelphia chromosome-positive disease (e.g., imatinib, dasatinib, nilotinib, bosutinib, ponatinib)
      iii. In combination with cyclophosphamide, dexamethasone, vincristine, methotrexate, and cytarabine with or without blinatumomab

5. Member will not receive more than 6 treatment cycles of the requested drug.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested drug.
B. The requested drug is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen.
D. Member has not/will not receive more than 6 treatment cycles of the requested drug.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Besponsa.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Pediatric acute lymphoblastic leukemia
4. NCCN Guideline: Acute lymphoblastic leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Besponsa are covered in addition to pediatric acute lymphoblastic leukemia.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Besponsa to treat pediatric acute lymphoblastic leukemia can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Besponsa [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals LLC, Inc.; March 2018.
2. Kantarjian Hagop M, DeAngelo Daniel J., Stelljes Matthias, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med.* 2016; 375: 740-53
3. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 5, 2023.

BLINCYTO (blinatumomab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Blincyto is indicated for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and pediatric patients.
   2. Blincyto is indicated for the treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and pediatric patients.

B. Compendial Uses
   Acute lymphoblastic leukemia (ALL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For initial requests: Testing or analysis confirming CD19 protein on the surface of the B cell

III. CRITERIA FOR INITIAL APPROVAL

B-cell Precursor Acute Lymphoblastic Leukemia
Authorization of 9 months may be granted for treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) when one of the following criteria are met:
A. The requested medication will be used as consolidation or maintenance therapy.
B. The requested medication will be used for relapsed or refractory disease.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
   1. No evidence of unacceptable toxicity while on the current regimen and
   2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Blincyto.

2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Acute lymphoblastic leukemia
4. NCCN Guideline: Pediatric acute lymphoblastic leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Blincyto and are included in addition to acute lymphoblastic leukemia.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for acute lymphoblastic leukemia and pediatric acute lymphoblastic leukemia can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Blincyto [package insert]. Thousand Oaks, CA: Amgen Inc.; June 2023.
2. The NCCN Drugs & Biologics Compendium 2022 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed May 23, 2023.
3. External Infusion Pumps (L33794) Version R29. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed October 2, 2023.

VELCADE (bortezomib)
bortezomib

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Treatment of adult patients with multiple myeloma
2. Treatment of adult patients with mantle cell lymphoma

B. Compendial Uses
1. Systemic light chain amyloidosis
2. Waldenström macroglobulinemia/lymphoplasmacytic lymphoma
3. Multicentric Castleman disease
4. Adult T-cell leukemia/lymphoma
5. Antibody mediated rejection of solid organ
6. Acute lymphoblastic leukemia
7. Follicular lymphoma
8. Kaposi sarcoma
9. Pediatric Classic Hodgkin Lymphoma
10. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome
11. Peripheral T-cell Lymphomas
    a. Anaplastic large cell lymphoma
    b. Peripheral T-cell lymphoma not otherwise specified
    c. Angioimmunoblastic T-cell lymphoma
    d. Enteropathy-associated T-cell lymphoma
    e. Monomorphic epitheliotropic intestinal T-cell lymphoma
    f. Nodal peripheral T-cell lymphoma with TFH phenotype
    g. Follicular T-cell lymphoma
12. Breast implant-associated anaplastic large cell lymphoma (ALCL)
13. Hepatosplenic T-cell lymphoma
14. Mycosis fungoides/Sezary syndrome
15. HIV-related B-cell lymphomas
    a. HIV-related diffuse large B-cell lymphoma
    b. HHV8-positive diffuse large B-cell lymphoma not otherwise specified
    c. Primary effusion lymphoma
16. Desensitization therapy – heart transplant

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Multiple myeloma
Authorization of 12 months may be granted for the treatment of multiple myeloma.

B. Mantle cell lymphoma
Authorization of 12 months may be granted for the treatment of mantle cell lymphoma.

C. Multicentric Castleman disease
Authorization of 12 months may be granted for the treatment of multicentric Castleman disease as subsequent therapy.

D. Systemic light chain amyloidosis
Authorization of 12 months may be granted for the treatment of systemic light chain amyloidosis.

E. Waldenström macroglobulinemia/lymphoplasmacytic lymphoma
Authorization of 12 months may be granted for the treatment of Waldenström macroglobulinemia/lymphoplasmacytic lymphoma.

F. Peripheral T-cell lymphomas
Authorization of 12 months may be granted as a single agent for the treatment of any of the following peripheral T-cell lymphomas:
1. Anaplastic large cell lymphoma (ALCL)
2. Peripheral T-cell lymphoma not otherwise specified
3. Angioimmunoblastic T-cell lymphoma
4. Enteropathy-associated T-cell lymphoma
5. Monomorphic epitheliotropic intestinal T-cell lymphoma
6. Nodal peripheral T-cell lymphoma with TFH phenotype
7. Follicular T-cell lymphoma

G. Adult T-cell Leukemia/Lymphoma
Authorization of 12 months may be granted for the treatment of adult T-cell leukemia/lymphoma when the requested medication will be used as a single agent for subsequent therapy.

H. Breast implant-associated ALCL
Authorization of 12 months may be granted for the treatment of breast implant-associated ALCL when the requested medication will be used as a single agent for subsequent therapy.

I. Hepatosplenic T-cell lymphoma
Authorization of 12 months may be granted for the treatment of hepatosplenic T-cell lymphoma when the requested medication will be used as a single agent for refractory disease.

J. Mycosis fungoides/Sezary syndrome
Authorization of 12 months may be granted for the treatment of mycosis fungoides/Sezary syndrome when the requested medication will be used as a single agent for refractory disease.

K. HIV-related B-cell lymphomas
Authorization of 12 months may be granted for the treatment of HIV-related B-cell lymphomas when both of the following criteria are met:
1. The member has one of the following lymphomas:
    a. HIV-related diffuse large B-cell lymphoma
    b. HHV8-positive diffuse large B-cell lymphoma, not otherwise specified
    c. Primary effusion lymphoma
2. The requested drug will be used as a component of bortezomib-ICE (ifosfamide, carboplatin, and etoposide)

L. Antibody mediated rejection of solid organ
Authorization of 12 months may be granted for the treatment of antibody mediated rejection of solid organ.

M. Acute lymphoblastic leukemia
Authorization of 12 months may be granted for the treatment of acute lymphoblastic leukemia.

N. Follicular Lymphoma
Authorization of 12 months may be granted for the treatment of relapsed or refractory follicular lymphoma.

O. Kaposi sarcoma
Authorization of 12 months may be granted for the treatment of Kaposi sarcoma as subsequent therapy.

P. Pediatric Classic Hodgkin Lymphoma
Authorization of 12 months may be granted for the treatment of relapsed or refractory Pediatric Classic Hodgkin Lymphoma.

Q. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome
Authorization of 12 months may be granted for treatment of POEMS syndrome in combination with dexamethasone.

R. Desensitization therapy – heart transplant
Authorization of 12 months may be granted for desensitization therapy for heart transplantation.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen, and
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Velcade and bortezomib.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Waldenstrom Macroglobulinemia/Lymphoplasmacytic lymphoma
4. NCCN Guideline: Systemic light chain amyloidosis
5. NCCN Guideline: Multiple myeloma
6. NCCN Guideline: T-cell lymphomas
7. NCCN Guideline: Pediatric Hodgkin lymphoma
8. NCCN Guideline: Kaposi sarcoma
9. NCCN Guideline: Pediatric acute lymphoblastic leukemia
10. NCCN Guideline: B-cell lymphomas
11. NCCN Guideline: Acute lymphoblastic leukemia
12. Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care
13. International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients.
14. Review of bortezomib treatment of antibody-mediated rejection in renal transplantation

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Velcade are covered in addition to the following:
1. Systemic light chain amyloidosis
2. Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
3. Multicentric Castleman's disease
4. Adult T-cell leukemia/lymphoma
5. Antibody-mediated rejection of solid organ

6. Acute lymphoblastic leukemia
7. Follicular lymphoma
8. Kaposi sarcoma
9. Pediatric Classic Hodgkin lymphoma
10. POEMS syndrome
11. Peripheral T-cell lymphomas
    A. Anaplastic large cell lymphoma
    B. Peripheral T-cell lymphoma not otherwise specified
    C. Angioimmunoblastic T-cell lymphoma
    D. Enteropathy-associated T-cell lymphoma
    E. Monomorphic epitheliotropic intestinal T-cell lymphoma
    F. Nodal peripheral T-cell lymphoma with TFH phenotype
    G. Follicular T-cell lymphoma
12. Breast implant-associated anaplastic large cell lymphoma
13. Hepatosplenic T-cell lymphoma
14. Mycosis fungoides/Sezary syndrome
15. HIV-related B-cell lymphomas
    1. HIV-related diffuse large B-cell lymphoma
    2. HHV8-positive diffuse large B-cell lymphoma not otherwise specified
    3. Primary effusion lymphoma
16. Desensitization therapy- heart transplant

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using bortezomib to treat systemic light chain amyloidosis, Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma, multicentric Castleman's disease, adult T-cell leukemia/lymphoma, acute lymphoblastic leukemia, follicular lymphoma, Kaposi sarcoma, pediatric classic Hodgkin lymphoma, peripheral T-cell lymphoma, breast implant-associated anaplastic large cell lymphoma, hepatosplenic T-cell lymphoma, mycosis fungoides/Sezary syndrome, and HIV-related B-cell lymphomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using bortezomib in the treatment of antibody mediated rejection can be found in the Canadian Cardiovascular Society and Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care. The position statement indicates providers can consider adjunctive rituximab and/or bortezomib for treatment of antibody-mediated rejection.
Roberts et al conducted a systematic review to determine the efficacy of treatments for acute antibody-mediated rejection in kidney transplant recipients. The randomized studies were small (median, 13 patients/arm; range, 5-23), of which, four examined plasmapheresis (one suggested benefit) and one for immunoadsorption (also suggesting benefit). Marked heterogeneity was evident, including the definition and severity of AMR and the treatment regimen. The end point of graft survival was common to all studies. Small, nonrandomized controlled studies suggested benefit from rituximab or bortezomib. The effects of dose and regimen on the clinical response to any of the current treatments were not apparent from the available data. Data describing the efficacy of treatments for AMR in renal allografts are of low or very low quality. Larger randomized controlled trials and dose-response studies are required.
The International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients states the treatment of moderate to severe AMR can include plasmapheresis with or without anti-B cell agents such as rituximab, bortezomib, or eculizumab (Quality/Certainty of Evidence: Moderate; Strength of Evidence: Conditional).

Support for using bortezomib as desensitization therapy to facilitate heart transplantation can be found in the Canadian Cardiovascular Society and Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care. The position statement indicates intravenous immune globulin, rituximab and bortezomib form the foundation of desensitization treatments.

Bortezomib should be considered if the patient has a poor response to rituximab desensitization therapy. Most pre transplantation desensitization protocols include IVIG 2 g/kg divided over 2 days (and continued monthly) with the additional use of rituximab in either a single 375 mg/m2 or 1 g dose. Effective B-cell depletion can be assessed by measuring lymphocyte cell subsets 2 days post administration with target CD19 < 2%. If there is no reduction in antibody after 3 months, alternative therapies such as bortezomib and eculizumab may be considered. Concurrent plasmapheresis may be reserved for short-term antibody depletion peri-, intra-, and postoperatively.

Support for using bortezomib in POEMS syndrome can be found in the National Comprehensive Cancer Network's guideline for multiple myeloma. The NCCN Guideline for multiple myeloma supports the use of bortezomib in combination with dexamethasone as either induction therapy for transplant eligible patients or for transplant ineligible patients.

VI. REFERENCES

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Botulinum Toxins

BOTOX (onabotulinumtoxinA)
DYSPORT (abobotulinumtoxinA)
XEOMIN (incobotulinumtoxinA)
MYOBLOC (rimabotulinumtoxinB)
DAXXIFY (daxibotulinumtoxinA-lanm)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. BOTOX

1. FDA-Approved Indications
   a. Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
   b. Treatment of urinary incontinence due to detrusor muscle overactivity associate with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication
   c. Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with a headache lasting 4 hours a day or longer)
   d. Treatment of spasticity in patients 2 years of age and older
   e. Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain
   f. Treatment of severe primary axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
   g. Treatment of blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients ≥ 12 years of age
   h. Treatment of strabismus in patients ≥ 12 years of age
   i. Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication

2. Compendial Uses
   a. Achalasia
   b. Auriculotemporal syndrome
   c. Backache
   d. Benign prostatic hyperplasia
   e. Cervicogenic headache
   f. Chronic anal fissures
   g. Congenital esotropia
   h. Detrusor and sphincter dyssynergia
   i. Difficulty speaking after total laryngectomy
   j. Disorder of esophagus
   k. Epicondylitis
   l. Essential tremor disorder
   m. Excessive salivation secondary to advanced Parkinson's disease
   n. Excessive salivation secondary to a disorder of the nervous system
   o. Excessive tear production
   p. Fibromyalgia
   q. Gilles de la Tourette's syndrome
   r. Granuloma of vocal cords which is refractory to conventional surgical and medical therapies
   s. Hemifacial spasm

t. Isolated oromandibular dystonia
u. Larynx closure as adjunct to surgical procedure
v. Myofascial pain syndrome
w. Oculomotor nerve injury
x. Organic voice tremor
y. Palmar hyperhidrosis
z. Pelvic floor dyssynergia
aa. Pharyngoesophageal segment spasm following total laryngectomy
bb. Refractory idiopathic trigeminal neuralgia
cc. Spastic dysphonia
dd. Stuttering
ee. Tardive dyskinesia
ff. Temporomandibular joint disorder
gg. Tension-type headache
hh. Thoracic outlet syndrome
ii. Whiplash injury to neck

B. DYSPORT

1. FDA-Approved Indications
   a. Treatment of adults with cervical dystonia
   b. Treatment of spasticity in patients 2 years of age and older

2. Compendial Uses
   a. Achalasia in patients who are surgical candidates
   b. Blepharospasm
   c. Hemifacial spasm

C. XEOMIN

FDA-Approved Indications

1. Treatment of chronic sialorrhea in patients 2 years of age and older
2. Treatment of upper limb spasticity in adult patients
3. Treatment of upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy
4. Treatment of adults with cervical dystonia
5. Treatment of adults with blepharospasm

D. MYOBLOC

1. FDA-Approved Indication
   a. Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia
   b. Treatment of chronic sialorrhea in adults

2. Compendial Uses
   a. Axillary hyperhidrosis
   b. Bladder muscle dysfunction leading to overactive bladder
   c. Bladder spasticity secondary to a spinal cord injury
   d. Blepharospasm
   e. Hemifacial spasm
   f. Palmar hyperhidrosis
   g. Spastic dysphonia
   h. Upper limb spasticity

E. DAXXIFY

1. FDA-Approved Indication
   a. The treatment of cervical dystonia in adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

Coverage will not be provided for cosmetic use.

III. CRITERIA FOR INITIAL APPROVAL

A. BOTOX

1. **Overactive bladder with urinary incontinence**
   Authorization of 12 months may be granted for the treatment of overactive bladder in adults, 18 year of age and older with urinary incontinence.

2. **Urinary incontinence associated with a neurologic condition**
   Authorization of 12 months may be granted for the treatment of urinary incontinence associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) when members are 5 years of age and older.

3. **Chronic migraine prophylaxis**
   Authorization of 6 months (two injection cycles) may be granted for the treatment of chronic migraine headache when all of the following are met:
   1. Member has migraine headaches at least 15 days per month.
   2. Member is 18 years of age or older.

4. **Limb spasticity**
   Authorization of 12 months may be granted for the treatment of limb spasticity including hands and feet either as a primary diagnosis or as a symptom of a condition causing limb spasticity in members 2 years of age and older.

5. **Cervical dystonia**
   Authorization of 12 months may be granted for the treatment of adults with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck when members are 18 years of age or older.

6. **Primary axillary hyperhidrosis**
   Authorization of 12 months may be granted for the treatment of primary axillary hyperhidrosis for members 18 years of age and older.

7. **Blepharospasm**
   Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm when the member is 12 years of age or older.

8. **Strabismus**
   Authorization of 12 months may be granted for the treatment of strabismus when the member is 12 years of age or older.

9. **Achalasia**
   Authorization of 12 months may be granted for the treatment of achalasia.

10. **Auriculotemporal syndrome**
    Authorization of 12 months may be granted for the treatment of auriculotemporal syndrome.

11. **Backache**

Authorization of 6 months may be granted for the treatment of chronic lower back pain.

12. **Benign prostatic hyperplasia**
    Authorization of 12 months may be granted for the treatment of benign prostatic hyperplasia.

13. **Cervicogenic headache**
    Authorization of 12 months may be granted for the treatment of cervicogenic headache.

14. **Chronic anal fissures**
    Authorization of 12 months may be granted for the treatment chronic anal fissures.

15. **Congenital esotropia**
    Authorization of 12 months may be granted for the treatment of congenital esotropia.

16. **Detrusor (including neurogenic detrusor overactivity (NDO)) and sphincter dyssynergia**
    Authorization of 12 months may be granted for the treatment of detrusor (NDO) and sphincter dyssynergia.

17. **Difficulty speaking after total laryngectomy**
    Authorization of 12 months may be granted for the treatment of difficulty speaking following a total laryngectomy.

18. **Disorder of esophagus**
    Authorization of 12 months may be granted for the treatment of disorder of the esophagus.

19. **Epicondylitis**
    Authorization of 12 months may be granted for the treatment of epicondylitis.

20. **Essential tremor**
    Authorization of 12 months may be granted for the treatment of disorder of essential tremor.

21. **Excessive salivation secondary to a disorder of the nervous system or advanced Parkinson's disease**
    Authorization of 12 months may be granted for the treatment of excessive salivation secondary to a disorder of the nervous system or advanced Parkinson's disease.

22. **Excessive tear production**
    Authorization of 12 months may be granted for the treatment of excessive tear production.

23. **Fibromyalgia**
    Authorization of 12 months may be granted for the treatment of fibromyalgia.

24. **Gilles de la Tourette's syndrome**
    Authorization of 12 months may be granted for the treatment of Gilles de la Tourette's syndrome.

25. **Granuloma of vocal cords**
    Authorization of 12 months may be granted for the treatment of granuloma of the vocal cords that is refractory to conventional surgical and medical therapies.

26. **Hemifacial spasm**
    Authorization of 12 months may be granted for the treatment of hemifacial spasm.

27. **Idiopathic trigeminal neuralgia**
    Authorization of 12 months may be granted for the treatment of refractory idiopathic trigeminal neuralgia.

28. **Isolated oromandibular dystonia**
    Authorization of 12 months may be granted for the treatment of isolated oromandibular dystonia.

29. **Larynx closure as adjunct to surgical procedure**
    Authorization of 12 months may be granted for the treatment of larynx closure as adjunct to surgical procedure.

30. **Myofascial pain syndrome**
    Authorization of 12 months may be granted for the treatment of myofascial pain syndrome.

31. **Oculomotor nerve injury**
    Authorization of 12 months may be granted for the treatment of oculomotor nerve injury.

32. **Organic voice tremor**
    Authorization of 12 months may be granted for the treatment of organic voice tremor.

33. **Palmar hyperhidrosis**
    Authorization of 12 months may be granted for the treatment of palmar hyperhidrosis.

34. **Pelvic floor dyssynergia**
    Authorization of 12 months may be granted for the treatment of pelvic floor dyssynergia.

35. **Pharyngoesophageal segment spasm following total laryngectomy**
    Authorization of 12 months may be granted for the treatment of pharyngoesophageal segment spasm following total laryngectomy.

36. **Spastic dysphonia**
    Authorization of 12 months may be granted for the treatment of spastic dysphonia.

37. **Stuttering**
    Authorization of 12 months may be granted for the treatment of stuttering.

38. **Tardive dyskinesia**
    Authorization of 12 months may be granted for the treatment of tardive dyskinesia.

39. **Temporomandibular joint disorder**
    Authorization of 12 months may be granted for the treatment of temporomandibular joint disorder.

40. **Tension-type headache**
    Authorization of 12 months may be granted for the treatment of tension-type headache.

41. **Thoracic outlet syndrome**
    Authorization for 12 months may be granted for the treatment of thoracic outlet syndrome.

42. **Whiplash to the neck**
    Authorization of 12 months may be granted for the treatment of whiplash to the neck.

B. DYSPORT

1. **Cervical dystonia**
   Authorization of 12 months may be granted for the treatment of adults 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck.

2. **Limb spasticity**
   Authorization of 12 months may be granted for the treatment of upper or lower limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity in members 2 years of age or older.

3. **Achalasia**
   Authorization of 12 months may be granted for the treatment of achalasia.

4. **Blepharospasm**
   Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm.

5. **Hemifacial spasm**
   Authorization of 12 months may be granted for hemifacial spasm.

C. XEOMIN

1. **Blepharospasm**
   Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm in members 18 years of age or older.

2. **Cervical dystonia**
   Authorization of 12 months may be granted for the treatment of adults, aged 18 years and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck.

3. **Upper limb spasticity**
   Authorization of 12 months may be granted for the treatment of upper limb spasticity when all of the following are met:
   1. Member has a diagnosis of upper limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity
   2. Member meets one of the following criteria:
      a. Member is 18 years of age or older
      b. Member is 2 to 17 years of age and the spasticity is not caused by cerebral palsy.

4. **Excessive salivation**
   Authorization of 12 months may be granted for the treatment of excessive salivation (chronic sialorrhea) for members 2 years of age and older.

D. MYOBLOC

1. **Cervical dystonia**
   Authorization of 12 months may be granted for the treatment of adults, aged 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of head and limited range of motion in the neck.

2. **Axillary hyperhidrosis**
   Authorization of 12 months may be granted for the treatment of primary axillary hyperhidrosis.

3. **Overactive bladder with urinary incontinence**
   Authorization of 12 months may be granted for the treatment of overactive bladder with urinary incontinence.

4. **Bladder spasticity secondary to a spinal cord injury**
   Authorization for 12 months may be granted for the treatment of bladder spasticity secondary to a spinal cord injury.

5. **Blepharospasm**
   Authorization of 12 months may be granted for the treatment of blepharospasm.

6. **Excessive salivation**
   Authorization of 12 months may be granted for the treatment of excessive salivation (chronic sialorrhea) in adults aged 18 years and older.

7. **Hemifacial spasm**

Authorization of 12 months may be granted for hemifacial spasm.

8. **Palmar hyperhidrosis**
   Authorization of 12 months may be granted for the treatment of palmar hyperhidrosis.

9. **Spastic dysphonia**
   Authorization of 12 months may be granted for the treatment of spastic dysphonia.

10. **Upper limb spasticity**
    Authorization of 12 months may be granted for the treatment of upper limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity.

E. DAXXIFY

1. **Cervical dystonia**
   Authorization of 12 months may be granted for the treatment of adults, aged 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of head and limited range of motion in the neck.

III. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for all members (including new members) who are continuing with botulinum toxin therapy when the following criteria are met:
1. The member is currently receiving therapy with the requested botulinum toxin drug.
2. The botulinum toxin drug requested is for a diagnosis or condition enumerated in Section II.
3. The botulinum toxin drug requested has been effective for treating the diagnosis or condition.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Botox, Daxxify, Dysport, Myobloc, and Xeomin.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. European Academy of Neurology guideline on trigeminal neuralgia
4. Practice guideline update: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adults spasticity, and headache: report of the guideline development subcommittee of the American Academy of Neurology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Botox, Daxxify, Dysport, Myobloc and Xeomin are covered in addition to the following:
A. Botox
1. Achalasia
2. Auriculotemporal syndrome
3. Backache
4. Benign prostatic hyperplasia
5. Cervicogenic headache
6. Chronic anal fissures
7. Congenital esotropia
8. Detrusor and sphincter dyssynergia
9. Difficulty speaking after total laryngectomy
10. Disorder of esophagus
11. Epicondylitis
12. Essential tremor disorder

13. Excessive salivation secondary to advanced Parkinson’s disease
14. Excessive salivation secondary to a disorder of the nervous system
15. Excessive tear production
16. Fibromyalgia
17. Gilles de la Tourette's syndrome
18. Granuloma of vocal cords which is refractory to conventional surgical and medical therapies
19. Hemifacial spasm
20. Isolated oromandibular dystonia
21. Larynx closure as adjunct to surgical procedure
22. Myofascial pain syndrome
23. Oculomotor nerve injury
24. Organic voice tremor
25. Palmar hyperhidrosis
26. Pelvic floor dyssynergia
27. Pharyngoesophageal segment spasm following total laryngectomy
28. Refractory idiopathic trigeminal neuralgia
29. Spastic dysphonia
30. Stuttering
31. Tardive dyskinesia
32. Temporomandibular joint disorder
33. Tension-type headache
34. Thoracic outlet syndrome
35. Whiplash injury to neck

B. Dysport
1. Achalasia in patients who are surgical candidates
2. Blepharospasm
3. Hemifacial spasm

C. Myobloc
1. Axillary hyperhidrosis
2. Bladder muscle dysfunction leading to overactive bladder
3. Bladder spasticity secondary to a spinal cord injury
4. Blepharospasm
5. Hemifacial spasm
6. Palmar hyperhidrosis
7. Spastic dysphonia
8. Upper limb spasticity

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using Botox to treat achalasia can be found in a trial by Annese and Bassotti. A double-blind, placebo-controlled trial verified the efficacy of botulinum toxin for previously untreated achalasia. Sixteen patients were randomized to placebo or botulinum toxin, endoscopically injected into multiple sites within the lower esophageal sphincter (total of 100 units as 0.5-mL aliquots of 12.5 units each). All patients in the botulinum group reported significantly improved mean symptom scores at the one-month visit. In contrast, all placebo-treated patients had unchanged symptom scores and required pneumatic dilation. When comparing pneumatic dilation to botulinum toxin, statistically similar reductions in symptom score, sphincter pressure and esophageal retention occurred. The beneficial effect of botulinum toxin lasted for a mean of 7.1 months and 10.8 months after the first and second injections, respectively.
Additionally, Kolbasnik and colleagues published one study of 30 consecutive patients. The authors reported an initial 77% response rate, with 30% of responders maintaining symptom relief after a single 80-unit injection for a mean of 21 months. Of the remaining 70% of responders who relapsed (at 11 months on average), 56% were successfully treated with additional injection(s). Those who failed the first botulinum toxin injection also failed subsequent injections. Reduction of lower esophageal sphincter pressure to less than 18 mmHg at one-month postinjection was a significant predictor of symptomatic response.

Support for using Botox to treat auriculotemporal syndrome can be found in a study by Duluerov et al. Local infiltration of botulinum toxin was effective in reducing food-induced facial flushing and sweating in 15 patients with Frey syndrome. Patients received total doses of 15 to 75 units, given as 0.1-mL injections with a 1-cm inter-injection distance. An evaluation 2 weeks later demonstrated a significant reduction in sweat quantity as compared with baseline (p less than 0.05). Measurements of skin temperature and color (erythema) did not show a clear difference before and after treatment. Subjectively, symptoms were reported to disappear in all patients following treatment. No adverse effects were reported.

Support for using Botox to treat backache can be found in a study by Foster et al. Botulinum toxin type A administered paravertebrally was effective in relieving pain and improving function in patients with chronic lower back pain. Patients (n=31) were randomized to 200 units of Botox(R) (40 units per site at 5 lumbar paravertebral levels) on the side of maximum discomfort (n=15) or to placebo (n=16). At 3 weeks, 73.3% of patients receiving botulinum toxin had more than 50% pain relief compared with 25% in the placebo group (p equal to 0.012). At 8 weeks, 60% of the patients receiving botulinum toxin experienced relief compared with 12.5% in the placebo group (p equal to 0.009). A questionnaire on physical impairment and disability was given at 8 weeks and 66.7% patients in the botulinum toxin group showed improvement compared with 18.8% in the placebo group (p equal to 0.011). There were no side effects reported.

Support for using Botox to treat benign prostatic hyperplasia can be found in a study by Maria et al. A randomized, double-blind study demonstrated that botulinum toxin type A (Botox(R)) was significantly more effective than placebo for the treatment of benign prostatic hyperplasia (BPH). Patients with symptomatic BPH who no longer responded to medication and refused surgical treatment were randomized to receive botulinum toxin A injection (n=15) or placebo injection (n=15). Inclusion criteria were moderate to severe symptoms of urinary obstruction based on the American Urological Association (AUA) index, mean peak urinary flow rate less than 15 mL/sec with voided volume of at least 150 mL, and an enlarged prostate gland. Primary study endpoints were the AUA symptom score and peak urinary flow rate. Each patient received an injection of 4 mL of solution into the prostate (2 mL into each lobe of the gland); the placebo group received saline solution only and the botulinum toxin A group received 200 Units of botulinum toxin type A. At both the 1-month and 2-month evaluations, patients in the botulinum toxin A group demonstrated significant improvement in all measures compared with baseline and to the placebo group. At 1 month, 11 of 15 patients in the botulinum toxin A group and 2 of 15 in the placebo group had symptomatic relief. In the botulinum toxin A group, the mean AUA score decreased from 23.2 at baseline to 10.6 posttreatment (54% decrease; p=0.00001) and mean peak urinary flow rate increased from 8.1 mL/sec to 14.9 mL/sec (p=0.00001). At the 2-month evaluation, 13 patients in the botulinum toxin A group and 3 in the placebo group had symptomatic relief; the botulinum toxin A group had a 65% decrease in mean AUA score (p=0.00001) and the mean peak urinary flow rate was 15.4 mL/sec (p=0.00001). At both evaluation time points, these post-injection measures did not change significantly from baseline in the placebo group and were significantly different from the botulinum toxin A group (p not stated). For the patients who received a botulinum toxin A injection, improvements in all outcome measures were maintained at 6 and 12-month evaluations. No adverse events were reported during the follow-up period (average duration 19.6 months).

Support for using Botox to treat cervicogenic headache can be found in a study by Freund and Schwartz. In a randomized, double blind, placebo-controlled pilot study, the efficacy of botulinum toxin A in reducing the pain associated with cervicogenic headache was tested in 30 otherwise healthy subjects ranging in age from 29 to 75 years. Patients were included if they suffered from chronic headache unrelieved by other therapies secondary to a cervical whiplash injury which occurred within 2 years of study entry and which restricted range of motion in the neck. Each patient was given an injection of botulinum toxin A (100 units diluted in 1 mL saline) or an equivalent volume of saline placebo dispersed in the five most tender cervical muscular trigger points. At 2 and 4 weeks later, the patients were evaluated for neck range of motion and for pain using a 10-point visual analog scale. At 2 weeks, the range of motion had increased for the treatment group (no p value reported). There was no significant change in the placebo group. At 4 weeks, both median pain scores and range of motion degree measurements improved significantly from preinjection levels for the group treated with botulinum toxin A (p=0.01). No significant change from baseline was seen in the placebo group. A potential confounder in this study was the difference in pain scores between groups at baseline. The median headache pain score for the placebo group was 3 (on a scale from 0 to 10), while that of the treatment group was 6.5 (no statistics reported). Thus, the placebo group appeared to have less headache pain, and therefore less room to improve, at the start of the trial. No side effects attributable to botulinum toxin A were reported in this study.

Support for using Botox to treat chronic anal fissures can be found in several published studies. Mentes et al. found botulinum toxin type A had a lower, shorter-term healing rate but significantly better recovery and adverse effect profile than lateral internal sphincterotomy (LIS) for the treatment of chronic anal fissure. Patients with severe, chronic fissure with visible horizontal fibers in the base of the internal anal sphincter were randomly selected to receive botulinum toxin type A (Botox(R)) injection (n=61) or LIS (n=50). For the botulinum toxin group (BT), patients received 0.3 units per kg injected in equal volumes on either side of the anterior midline; treatment was repeated if there was non- or incomplete healing 2 months after the first injection. Healing rate, defined as complete healing of the fissure, was significantly higher for the LIS group at 28 days (62.3% BT group vs 82% LIS group; p=0.023), 2 months (73.8% BT group vs 98% LIS group; p less than 0.0001), and 12 months posttreatment (75.4% BT group vs 94% LIS group; p=0.008). At 6 months posttreatment, healing rate was comparable between the groups (86.9% BT group vs 94% LIS group; p=0.212). Sixteen patients with incomplete healing in the BT group were offered repeat treatment; 6 refused due to satisfaction with pain relief from the first treatment and were considered incomplete healers in healing rate determinations. The BT group recovered from treatment significantly faster than the LIS group; return to daily activities averaged 1 day for the BT group and 14.8 days for the LIS group (p less than 0.0001). Complication rate was significantly different between the groups, no adverse events were reported in the BT group compared with 16% of patients in the LIS group reporting transient flatus incontinence (p less than 0.001).
Minguez et al successfully treated chronic anal fissure in a nonrandomized, prospective, dose-ranging trial (n=69). Dosing consisted of 5 units of botulinum toxin A on each side of the fissure (low dose: total 10 units), 5 units on each side of the fissure plus 5 units below the fissure (middle dose: total 15 units) or 7 units on each side of the fissure plus 7 units below the fissure (high dose: total 21 units). At 6 months follow-up, the overall rates of healing (83%, 78%, 90%), reinjection (52%, 30%, 37%) and sphincterotomy requirement (17%, 19%, 5%) did not differ statistically between the low, middle, and high dose groups, respectively. Adverse effects included puncture site infection (n=1), perianal hematoma (n=1) and transient flatus or fecal incontinence (n=7). All subjects were fully continent at the end of follow-up.

Support for using Botox to treat congenital esotropia can be found in a study by Campos, Schiavi and Bellusci. Botulinum toxin type A was effective in patients (n=60) with esotropia if treated by age 7 months. A minimum dose of 2.5 units of botulinum toxin type A per muscle was initially used in 10 patients but it was discovered that 3 units per muscle produced better results; therefore, the following 50 patients received the higher dose. The mean follow-up period was 5.2 years (2 to 9 years).

Support for using Botox to treat detrusor and sphincter dyssynergia can be found in a study by Gallien et al. Botulinum toxin A was not effective in treating detrusor sphincter dyssynergia (DSD) in patients with multiple sclerosis (MS) in a multicenter, double-blind, placebo-controlled clinical trial. Patients (n=86; mean age, 50 +/- 10 years) with DSD due to MS, who had post-voiding residual urine volumes between 100 and 500 mL were randomized to botulinum toxin A 100 units or placebo, administered as single transperineal injections using striated sphincter electromyography. Each patient was also started on an alpha-blocker (alfuzosin 5 mg slow-release twice daily) for 4 months. No significant differences were found in the primary endpoint, the post-voiding residual urine volume at day 30 (botulinum toxin A, 186 +/- 158 mL, n=43; placebo, 206 +/- 145 mL, n=40; p=0.45). Secondary endpoints that were assessed at day 30 included voiding variables (symptoms were assessed using 10 centimeter (cm) visual analogue scales) and urodynamic variables. Of the voiding variables, only the voiding volume was significantly improved (p=0.02) in the botulinum toxin A arm (197 +/- 143 mL; n=35) compared with the placebo arm (128 +/- 95 mL; n=34), while the other voiding variables (obstructive symptoms, pollakiuria, urgencies, incontinence, and International Prostatism Symptom Score) were no different between treatment groups. Urodynamic variables that were significantly improved in the botulinum toxin A arm compared with the placebo arm included pre-micturition detrusor pressure (botulinum toxin A, 24 +/- 11 cm of water, n=34; placebo, 34 +/- 18 cm of water, n=28; p=0.02) and maximal detrusor pressure (botulinum toxin A, 52 +/- 22 cm of water, n=35; placebo, 66 +/- 25 cm of water, n=32; p=0.02), while the other urodynamic variables (maximal and cloture urethral pressures, basal detrusor pressure, detrusor compliance, maximal bladder capacity, and maximal urinary flow) were no different between treatment groups. At time points between day 30 and day 120, few endpoints were significantly improved in the botulinum toxin A arm compared with the placebo arm; these included voiding volume (at days 30 and 60; p=0.05) and incontinence (between days 60 and 120; p=0.04). Adverse events were similar between treatment groups.

Support for using Botox to treat difficulty speaking after total laryngectomy can be found in two studies published by Blitzer and colleagues and Terrell and colleagues. Preliminary reports indicate that botulinum A toxin injection of the upper esophageal sphincter appears to be effective in the management of voice failure

after tracheoesophageal puncture (TEP) and prosthesis placement in most patients after total laryngectomy. Persistent focal constrictor hypertonicity/spasm appears to be responsible for the patients' poor speech production or inability to speak with the prosthesis. Botulinum A toxin injections of the cricopharyngeal muscle complex may be used successfully both diagnostically and therapeutically in patients who have voice production difficulties after TEP.

Support for using Botox to treat disorder of esophagus can be found in two studies. Alberty, Oelerich and Ludwig published a prospective study of patients with dysphagia. Botulinum toxin was effective in the treatment of dysphagia resulting from pure upper esophageal sphincter (UES) dysfunction. Ten patients (aged 39 to 77 years) with incomplete opening (n=8), delayed opening (n=1), or premature closure (n=1) of the UES received botulinum toxin 30 units injected into the UES under brief general anesthesia. One month following treatment, videofluoroscopic studies showed significant improvement in the opening of the pharyngoesophageal segment (from a mean of 47% at baseline to 71%, p less than 0.01). In addition, clinical symptoms scores improved in 9 of 10 patients (mean 4.9 at baseline to 2.0 post-injection).
Miller, Parkman, and Schiano published a study of fifteen patients with nonachalasia esophageal motility disorder, unresponsive to medical therapy, underwent endoscopic injection of botulinum toxin A at the level of the gastroesophageal junction. Twenty-unit injections were used in each of four quadrants above the squamocolumnar junction. There was significant improvement in chest pain (p less than 0.01), dysphagia (p less than 0.01), and regurgitation (p less than 0.01). After one month 73% of patients had a good or excellent response, while at the last patient interview (mean of 10.6 months) 33% continued to have a good to excellent response.

Support for using Botox to treat epicondylitis can be found in a study by Keizer et al. Botulinum toxin injection was as effective as surgical treatment for lateral humeral epicondylitis (tennis elbow) for patients who did not respond to conventional treatment. In this randomized pilot study, 40 patients received an injection of 30 to 40 units of botulinum toxin type A (Botox(R)) into the extensor carpi radius brevis (n=20) or a surgical wrist extensor release (Hohmann operation; n=20). Eight patients with insufficient paresis by the 6-week follow up received a second injection of botulinum toxin (50 units). Four of these patients still had insufficient paresis and had a Hohmann operation 6 to 18 months after initial treatment; only 1 of the 4 had a good result after surgery. During the 2-year follow up, the only significant difference between the groups was in the amount of sick leave at the 3-month follow-up, which was less in the operative group compared with the botulinum toxin group (p=0.01). The operative group experienced more extension problems of the elbow; 3 of 20 in the operative group and no patients in the botulinum toxin group had an extension deficit at the end of the 2-year follow-up. The overall results (modified Verhaar scoring system) showed no differences between the groups; 16 of 20 in the botulinum toxin group (15 of 16 for patients in botulinum toxin corrected group, with nonresponders excluded) and 17 of 20 in the operative group had treatment ratings of good or excellent. Botulinum toxin type A injection may provide a less invasive alternative for the treatment of tennis elbow.

Support for using Botox to treat essential tremor disorder can be found in a study by Brin et al. Botulinum toxin type A resulted in limited functional efficacy for the treatment of essential hand tremor since it improved postural but not kinetic hand tremors. Patients (n=133) with essential hand tremor were randomized to low-dose (50 units) or high-dose (100 units) botulinum toxin type A (Botox(R)) or placebo. Injections were made into the wrist flexors and extensors. During a 16-week follow-up, both doses of botulinum toxin significantly reduced postural tremor after 6 to 16 weeks (p=0.0002 and 0.0001 for low-dose and high-dose, respectively, at 6 weeks). Kinetic tremor, however, significantly reduced only at the 6-week examination (p=0.03 and 0.005 for low-dose and high-dose, respectively, at 6 weeks). Measures of motor tasks and functional disability were not consistently improved with treatment. In addition, grip strength was reduced for both doses of botulinum toxin type A compared with placebo. Dose-dependent hand weakness was the major adverse reaction reported.

Support for using Botox to treat excessive salivation secondary to advanced Parkinson’s disease can be found in two studies. Lagalla et al conducted a double-blind, randomized, placebo-controlled study (n=32), botulinum toxin type A was safe and led to subjective and objective improvement in drooling in outpatients with Parkinson disease. Nobrega et al conducted a open-label, prospective study. Ultrasound-guided, intraparotid injections of botulinum toxin type A decreased the severity, and to a limited extent, the frequency of diurnal drooling in outpatients with advanced Parkinson disease (PD) in an open-label, prospective study. Patients with PD characterized by presence of bradykinesia associated with muscular rigidity, 4 to 6 Hertz rest tremor, or postural instability were evaluated for sialorrhea. The drooling score was based on the sum of the scores for severity (1 to 5 scale; 1=dry: never drools; 5=profuse: clothing, hands, and tray moist wet) and frequency (1 to

4 scale; 1=never drools; 4=constant drooling). Patients (n=21; 18 males; mean age, 70 years; range, 55 to 84 years) with a diurnal sialorrhea of grade 5 or higher were included. Patients with dementia, severe depression, who had received treatment with neuroleptics within 1 years prior to onset of symptoms, or who had previously received treatment for drooling or anticholinergic drugs were among those excluded. Study patients were injected with botulinum toxin type A 125 units (500 units diluted in 2.5 mL saline) in two points of the parotid gland using ultrasonography. Drooling was evaluated by a speech therapist at 15 and 30 days following the injection. All patients were on levodopa therapy with entacapone and/or pramipexole during the study. At 15 days posttreatment, 19 of 21 patients reported a decrease in drooling; of the remaining 2 patients, one had no substantial change while the other's condition worsened. The total drooling score decreased from a mean baseline score of 6.85 to 5.14 at 1 month following the injection (p less than 0.001). The mean pre- and 1-month posttreatment drooling severity scores were 3.42 and 2.14, respectively (p less than 0.001), and drooling frequency scores were 3.42 and 3, respectively (p=0.021). Overall, the severity of drooling decreased in 18 (86%) patients and the frequency of drooling decreased in 8 (38%) patients. The frequency of drooling remained unchanged in 11 (52%) patients. Among treatment-emergent adverse events, two patients experienced mild dry mouth lasting 1 month. One patient developed bilateral local edema, which was mild, self-limited, and resolved after 4 days.

Support for using Botox to treat excessive salivation secondary to a disorder of the nervous system can be found in two published studies. Porta and colleagues found that ultrasound guided botulinum toxin type A was safe and effective in the treatment of sialorrhea in patients with neurological disorders. Botulinum toxin type A (Botox(R)) was injected bilaterally into the parotid and submandibular glands at doses which were calculated based on patient weight and rate of salivation. The mean parotid dose was 27.7 units/gland and the mean submandibular dose was 11.9 units/gland (mean total dose was 76.6 units). After treatment, there was a subjective reduction in salivation reported for 9 patients and no improvement in 1 patient. Visual analogue scale scores showed a 55% decrease in mean rate of salivation for all patients and a 61% decrease for the responder group. No serious adverse events occurred.
Additionally, Giess et al found that injections of botulinum toxin into the salivary glands successfully ameliorated sialorrhea and improved quality of life without significant adverse effects in patients with bulbar amyotrophic lateral sclerosis. Five patients (mean age 64 years) received 6 to 20 mouse units of botulinum toxin A injected into each parotid gland in 3 divided doses. This was repeated 2 weeks later if, as judged by the patient, the clinical response was inadequate. Additional injections (5 units) into each submandibular gland were required in 2 patients. In 4 of 5 patients, botulinum toxin injections markedly reduced sialorrhea as measured by paper handkerchiefs used before and at 4 weeks after treatment (11 vs 3, p=0.068) and by a reduced radiotracer uptake in both parotid glands noted on salivary gland scintigraphy. At up to 3 months of follow-up, a slight increase of sialorrhea was noted in 1 patient. Quality of life was markedly improved in 3 patients, moderately improved in 1 patient, and not enhanced in the last.

Support for using Botox to treat excessive tear production can be found in a study by Whittaker et al. A small pilot study demonstrated the effectiveness of botulinum toxin type A in the treatment of functional epiphora. Patients (n=14) with symptoms of epiphora and a patent lacrimal system received a single injection of 2.5 to 5 units of botulinum toxin A (Botox(R)) into the palpebral lobe of the lacrimal gland on the worst affected side. Four patients received 5 units of botulinum toxin A, but 2 of the 4 patients experienced side effects, so the remaining 10 patients received 2.5 units of botulinum toxin A. Evaluation of efficacy was based on a 5-minute Schirmer test and subjective reports from the patients at week 1, week 4, and week 13. A reduction in epiphora was reported by 71.4%, 85.7%, and 72.7% of patients at week 1, week 4, and week 13, respectively. Based on Schirmer test results, a reduction in tearing occurred in 78.6%, 71.4%, and 54.5% at week 1, week 4 and week 13, respectively. Adverse effects were reported in 2 patients who received a 5-unit botulinum toxin A dose; 1 patient had a ptosis that resolved within 4 weeks and another patient had vertical diplopia for 3 weeks after the injection. Additional studies to determine the optimal dosage as well as the safety and effectiveness of multiple injections over a longer term are recommended.

Support for using Botox to treat fibromyalgia and myofascial pain syndrome can be found in a study by Porta (1999). Botulinum A toxin exhibited efficacy equivalent or superior to that of methylprednisolone in the treatment of myofascial pain syndrome in a randomized, single-blind trial (n=40). Along with adjunctive bupivacaine, Botox(R) 80 to 150 units or methylprednisolone 80 mg was injected into the piriformis, scalenus anterior, or iliopsoas muscle as confirmed by computed tomography. All subjects also entered an intensive physiotherapy program. Visual analogue scores (VAS) for pain decreased significantly in both groups at 30 days versus baseline. Botulinum recipients recorded statistically lower mean VAS (2.3) as compared with

steroid recipients (4.9) at 60 days (p less than 0.0001). Neither regimen was associated with noteworthy adverse effects.

Support for using Botox to treat Gilles de la Tourette's syndrome can be found in a study by Kwak, Hanna and Jankovic. Botulinum toxin injections were effectively used to treat tics and associated premonitory symptoms in an open study of patients with Tourette syndrome. Thirty-five patients aged 8 to 69 years, who had a mean tic duration of 15 years, received an average of 120 units during each of 3 visits. The most common muscles injected were cervical, and those in the upper face, particularly the eyelids. During a mean follow-up period of 21 months (range 1.5 to 84 months), 29 patients experienced an improvement, with 23 of these patients demonstrating a marked improvement, based on a peak effect score of 3 or greater (0 to 4 scale). In addition, 21 (84%) of 25 patients with premonitory symptoms (described as discomfort, tingling, or tension preceding the tic) experienced significant relief from these symptoms. The duration of therapeutic benefits averaged 14 weeks. Adverse effects included neck weakness (n=4), ptosis (n=2), generalized weakness (n=1), dysphagia (n=2), fatigue (n=1), and nausea and vomiting (n=1).

Support for using Botox to treat granuloma of vocal cords which is refractory to conventional surgical and medical therapies can be found in a study by Orloff and Goldman. In a case series (n=8), botulinum A toxin (Botox(R)) was 100% effective in eradicating vocal fold granulomas that were refractory to conventional surgical and medical therapies. The toxin was injected under electromyographic guidance transcutaneously or during laryngoscopy into one or both thyroarytenoid muscles at an average dose of 10 units per site. All granulomas disappeared within 2 months. Four patients required early reinjection due to inadequate paresis. All patients remained free of recurrence throughout the follow-up period (11 to 41 months). Adverse effects included mild-to-moderate breathiness and reduced Valsalva effect in 7 and 1 patients, respectively. Depending on the etiology of vocal fold granuloma, treatment may also include voice therapy, behavioral modification and medication for contributory conditions (i.e., gastroesophageal reflux).

Support for using Botox to treat hemifacial spasm can be found in a retrospective chart review and open-label trial. In a retrospective chart review of 51 patients with benign essential blepharospasm (BEB, n=17), hemifacial spasm (HFS, n=17), or aberrant facial nerve regeneration synkinesis (AFR, n=17), and a minimum treatment period of 10 years, mean blepharospasm disability score (BDS) significantly improved from 6 to 3 at last review across all 3 groups, and improvement was significantly greater in patients receiving flexible-interval injections compared to fixed-interval injections (Bladen et al, 2019). Mean BDS improved significantly in the BEB group with a trend to improvement in the HFS and AFR group, and BDS improvement mainly occurred in the first year with smaller fluctuations in following years. Mean duration of maximal effect was 10.5 weeks across the 3 groups but increased progressively only in the flexible-interval group. Patients (mean age, 63 years) received injections at a fixed, 12-week interval (n=14; mean annual injections, 4) or at flexible intervals (n=37; mean annual injections, 3.4). The cumulative complication rate was the same in the flexible- and fixed-interval groups and included ptosis, dry eye, and lagophthalmos.
In an open-label, time series in adults with hemifacial spasm (n=137), serial treatment with onabotulinumtoxinA led to an overall response rate of 88%. Patients with right- or left-sided hemifacial spasm refractory to other forms of therapy received treatment (mean age, 56.3 +/- 13 years; 55% female; mean disease duration, 5.6 +/- 6.4 years) (Chen, 1996). Patients with a history of previous peripheral facial palsy were excluded. Most patients received a total of 12 to 15 units of onabotulinumtoxinA per injection, which was injected as follows: 2.5 units each into the central and lateral orbicularis oculi of the lower eyelid, 2.5 to 5 units into the lateral orbicularis oculi of the upper eyelid, and 5 units divided into the buccolabial and/or platysma muscles. However, 20 patients received a total dose of 25 units. Efficacy was assessed both objectively and subjectively prior to each injection and at each follow-up (2 weeks after the initial injection, then monthly until the subsequent injection). Objective assessment involved grading of clinical severity of spasm, by 2 assessors, using a 5-point scale (0=no abnormality/normal blinking to 4=severe prolonged disfigurement/incapacitating social activities) and videotape recording. Subjective assessment involved patient-report degree of spasm relief using a 5-point scale (0=baseline, 1=25% improvement, 2=50%, 3=75%, 4=more than 90% improvement). A total of 228 treatments were administered, with an average of 1.7 treatments per patient. Based on both objective and subjective measures, the overall response rate was 88% (57% substantial improvement and 31% improvement), and the overall mean duration of spasm relief was 20 weeks (range, 2 to 52 weeks). Only 4 patients achieved complete remission after the first injection, with most patients requiring subsequent treatments on average every 3 to 4 months. No significant difference in response rate was observed among those who received doses less than 15 units and those who received 15 units or more. Additionally, analysis of the first 5 treatments did not reveal a significant difference in the duration of spasm relief based on severity of pretreatment spasm. Among 216 treatments, the most common

adverse events included facial weakness in 95% of patients, which led to dynamic or static facial asymmetry in 37% of these patients, ptosis (29%), and diplopia (5%). Diplopia and ptosis resolved within 8 and 10 weeks, respectively, and the incidence decreased with consecutive treatments.

Support for using Botox to treat isolated oromandibular dystonia can be found in a several small open-label clinical trials. Jankovic and Hallett enrolled patients (n=96) who were diagnosed with jaw-closing OMD (n=51; 74.5% female), jaw-opening OMD (n=40; 67.5% female), or jaw-deviation OMD (n=5; 100% female) with over 70% of all cases considered idiopathic. Patients received botulinum toxin A (Botox(R)/Oculinum(R); Allergan Pharmaceuticals) into 3 to 5 sites of each involved muscle. Median doses for each muscle were 24.5 +/- 17.7 units (masseter; range, 2 to 100 units), 18.5 +/- 11.9 units (temporalis; range, 2 to 75 units), 16.3 +/- 8.1 units (medial pterygoid; range, 5 to 40 units), 15.9 +/- 8.7 (lateral pterygoid; range, 2.5 to 60 units), and 9.8 +/- 4.6 (anterior digastric; range, 3.75 to 30 units). Initial treatments were typically inadequate, and patients received an additional treatment of botulinum toxin A administered 2 to 4 weeks after the first dose. Patients rated their current condition using a linear, global clinical rating scale, with 0% defined as fully disabled/no useful function and 100% defined as normal. Patients with all 3 types of OMD reported statistically significant improvements, with improvements from 29.6% +/- 2.7% to 72% +/- 4.4% (p=0.0001) in the jaw-closing group, 30.8% +/- 4% to 73.8% +/- 4.2% (p=0.0001) in the jaw-opening group, and 38.8% +/- 9.2% to 75.8% +/- 12.2% (p=0.014) in the jaw-deviation group. Duration of benefit was 14.6 +/- 2.1 weeks, 11.8 +/- 2.1 weeks, and 10.8 +/- 5 weeks for the jaw-closing, jaw-opening, and jaw-deviation groups, respectively. Adverse effects occurred in 11.8% of patients in the jaw-closing group, 17.5% of patients in the jaw-opening group, and no patients in the jaw-deviation group. The most common adverse effect was dysphagia (n=14). One patient developed antibodies to botulinum toxin A.
Additionally, Jankovic, Schwartz, and Donovan studied patients (n=62; mean age, 57.2 years; range, 14 to 78 years) with idiopathic OMD, who despite optimal pharmacological therapy, surgery, or both, were treated with botulinum toxin A every 3 to 6 months, injected into masseters, submental, temporalis, and pterygoids muscles. Doses were initiated at 25 units per muscle and increased to 50 units each into the masseters and temporalis muscles. Assessments consisted of severity of dystonia (0 to 4 scale with 0 as no spasm and 4 as severe, incapacitating spasm) rated in a patient diary, latency (interval between the injection and first sign of improvement), peak effect (maximum benefit obtained; determined from patient diary, interview of family or friends, and patient's perception rated as no effect (0), mild improvement (1), moderate improvement but no change in function (2), moderate improvement in severity and function (3), or marked improvement in severity and function (4)), and global rating (peak effect score minus one point for mild or moderate complications or minus 2 points for severe or disabling complications). Patients received a total of 407 injections during 186 visits. Favorable response (global rating of 2 or more) occurred in 73% of evaluable patients (n=45) with OMD. Mean global rating was 2.2 +/- 1.5, while peak effect was 2.4 +/- 1.6, latency to response was 4.6 +/- 5.6 days (range, 0 to 30 days), and total duration of response was 10.3 +/- 8.7 weeks (range, 0 to 54 weeks). Over half (55.6%) of patients failed (global rating of 1 or less) one or more visits. Overall, adverse events were observed on 37% of visits (n=115) with the most common adverse event of dysphagia occurring in 12% of patients.

Support for using Botox to treat larynx closure as adjunct to surgical procedure can be found in a small study by Pototschnig et al (1996). In a small number of patients (n=6) requiring larynx closure, botulinum toxin A injections into the laryngeal musculature was effective at completely paralyzing the larynx and allowing for wound healing. Patients in this study all suffered from severe chronic aspiration caused by previous injury (e.g., stroke, tumor removal, and hypoxic trauma). Two weeks prior to surgery, patients were injected with 1 to 1.4 mL (200 to 280 units) of botulinum toxin A into the intrinsic laryngeal musculature (i.e., bilateral injections of posterior cricoarytenoid, aryepiglottic, medial thyroarytenoid, and lateral thyroarytenoid). Five of 6 patients had complete closure and the other patient had a thin fistula of the posterior commissure. This procedure reportedly preserves the ability of speech rehabilitation and can be performed in high-risk patients. Additional study is needed to further investigate the use of botulinum toxin A as adjunctive therapy to surgical procedures of the larynx.

Support for using Botox to treat oculomotor nerve injury can be found in a study by Talebnejad, Sharifi, and Nowroozzadeh. Botulinum toxin A injection was effective for treatment of trauma-induced, acute-phase, third nerve palsy (n=9). Additionally, Saad and Lee conducted a retrospective review of botulinum toxin A for the treatment of exotropia of third nerve palsy provides evidence that long-term efficacy may rely on pretreatment markers and that treatment is not a reliable predictor of surgical outcomes.

Support for using Botox to treat organic voice tremor can be found in a study Hertegard et al. Botulinum A toxin successfully ameliorated essential voice tremor in the majority of a case series (n=15, mean age 73

years). After injection into the bilateral thyroarytenoid muscles (dose range 0.6 to 5 units of Botox(R), typically at 3-month intervals), 67% of patients reported positive subjective results. Depending on the method of evaluation, the treatment was effective in 50% to 60% of patients. Adverse effects included transient breathiness, hoarseness and mild dysphagia.

Support for using Botox to treat palmar hyperhidrosis can be found in a study by Naver, Swartling and Aquilonius. Twenty-eight patients with palmar (n = 19) and/or axillary (n = 13) hyperhidrosis were treated with intracutaneous injections of botulinum toxin (Botox(R)) 2 U/4 cm2. Sweat function was studied clinically and by objective measurements after treatment of one side. Treated and untreated sides, and pre- and post-treatment skin areas were compared. Subjective evaluation was performed after treatment of one side and 2-5 months after treatment of both sides. Duration of effect was controlled by a one-year follow-up. Sweating disappeared in eight out of 13 patients with axillary and in five out of 19 with palmar hyperhidrosis and was reduced markedly in another five out of 13 and 10 out of 19 patients. Two-thirds of those treated for hand sweat noticed a slight and transient reduction of power of finger grip. No side-effects were noticed after treatment of axillary hyperhidrosis.

Support for using Botox to treat pelvic floor dyssynergia can be found in a study by Hallan et al. The group conducted an uncontrolled study involving 7 patients with constipation has suggested benefits of botulinum A toxin in the treatment of anismus in intractable constipation. Botulinum A toxin was injected into the puborectalis muscle (bilaterally), at a dose of 3 nanograms (ng) (1.5 ng on each side of the muscle). At 4 weeks following treatment, total symptoms scores improved significantly, and were correlated with a reduction in the maximum voluntary squeeze anal canal pressure and an increase in the anorectal angle upon straining. Clinical response was considered excellent in 4 of the patients, with repeat injections being given at 8 to 10 weeks. There was one complete failure and 2 partial failures. More studies are required under controlled conditions to evaluate the efficacy of botulinum A toxin in anismus, and to evaluate the efficacy and safety of administering the toxin over prolonged periods.

Support for using Botox to treat pharyngoesophageal segment spasm following total laryngectomy can be found in a study by Bartolomei et al. Treatment with botulinum A toxin plus participation in a voice therapy program led to improved phonation in a published case series of 34 patients with pharyngoesophageal segment spasm after laryngectomy. After the first patient failed to demonstrate a response with a dose of 20 units (who then received a repeat injection of 100 units), 26 patients received 100 units of botulinum A toxin, 3 patients with minor spasm received 50 units, 3 patients received 30 units, and 1 patient received 60 units. Doses were administered in 1 injection unilaterally (n=29) or bilaterally (n=1), or unilaterally in 6 to 7 divided injections (n=4). Electromyography was used to guide the injections in the pharyngeal constrictor muscles. Benefit was seen in all but 2 patients at 72 hours postinjection, and patients were able to count to 9, say their name, and speak short sentences. Rapid decline occurred in 8 patients, requiring botulinum A toxin injection every 3 months, while the other patients demonstrated long-lasting benefit. No adverse effects were reported except for mild dysphagia in 1 patient.

Support for using Botox to treat refractory idiopathic trigeminal neuralgia can be found in the European Academy of Neurology (Bendtsen, 2019). A weak recommendation for the addition of botulinum toxin type A to other medications for medium-term treatment of trigeminal neuralgia is based on very low-quality evidence. Liu et al published a study where botulinum toxin A significantly reduced visual analogue scale (VAS) pain scores from 8.5 to 4.5 in patients aged 80 years and older (n=14; mean age 82.6), and from 8 to 5 in patients less than 60-years-old (n=29; mean age 49.5). Patients were examined at baseline and at 1 month after treatment; median VAS scores were significantly lower at 1 month compared to baseline but did not differ significantly between groups. Drug administration was guided by pain and trigger zones and delivered transdermally and/or submucosally. Botulinum toxin A dosages were 45 to 150 units in the older group (mean, 91.3 units) and 30 to 200 units (mean, 71.8 units) in the younger group. Transient mild side effects occurred in 2 patients in each group and resolved spontaneously within 3 weeks.

Support for using Botox to treat spastic dysphonia can be found in a study published by Blitzer, Brin and Stewart. Based on 12 years of experience treating spasmodic dysphonia (6300 injections in 901 patients), botulinum A toxin is considered to be the treatment of choice. The types of dysphonia included adductor (82%), abductor (17%), and adductor breathing or paradoxical vocal fold motion (1%). Dosing of Botox(R) was individualized. For adductor dystonia, the average onset and duration were 2.4 days and 15 weeks, respectively, with patients achieving 90% of normal function. Corresponding values for abductor dystonia were 4 days, 10.5 weeks and 67%, respectively. Patients with adductor breathing dystonia returned to 82% of

normal functioning for a mean of 14 weeks. Botulinum A toxin was generally well-tolerated with a few patients developing mild and transient adverse effects such as breathiness, exertional wheezing/stridor and dysphagia.

Support for using Botox to treat stuttering can be found in a study by Brin, Stewart, and Blitzer. Botulinum A toxin 1.25 units (Botox(R)/Oculinum(R)) into each thyroarytenoid muscle has been shown to be effective in the treatment of stuttering with glottal block, resulting in a moderate improvement in fluency.

Support for using Botox to treat tardive dyskinesia can be found in an open-label study conducted by Rappaport et al. In an open-label study, the administration of botulinum toxin was effective and safe in the treatment of oro-facial-lingual-masticatory tardive dyskinesia due to dopamine receptor blocking agents. In this study, 12 psychiatric patients (mean age 74 years), who had received long-term treatment with phenothiazines or butyrophenones and were resistant to at least 1 prior treatment for dyskinesias, received 80 units of botulinum toxin injected subcutaneous into 4 facial sites (Lateral to the buccal commissures, midpoint of the upper lip, and the mid-central area of the chin). As assessed by the Tardive Dyskinesia Rating Scale, a significant improvement in dyskinesias was noted at 1, 5, and 8 weeks following treatment. A significant response was observed for pouting, grimacing, and dysarthria, while a trend for improvement was noted for puckering and choreoathetoid movements of the tongue. No adverse effects were observed.

Support for using Botox to treat temporomandibular joint disorder can be found in a study conducted by Freund, Schwartz, and Symington. A small, uncontrolled trial (n=15) provides preliminary evidence suggesting efficacy and safety of botulinum A toxin (Botox(R)) for chronic temporomandibular joint disorders. Subjects received a total of 150 units administered with electromyographic guidance to the masseter and temporalis muscles. When assessed every 2 weeks through week 8, average scores for pain, functional disability index, mouth opening, and tenderness improved from pretreatment values (p=0.05). Mean bite force did not change appreciably. Botulinum toxin therapy did not induce adverse effects or complications.

Support for using Botox to treat tension-type headache can be found in a several small trials. Porta (1999) reported headache pain scores were decreased by botulinum toxin to a greater extent than with methylprednisolone in a randomized, single-blind, comparative trial conducted in 20 patients ranging in age from 18 to 70 years. The subjects were recruited if they presented with a history of 2 or more tension-headache episodes per month for at least the past 3 months. They were then randomized to receive an IM injection of either 40 mg of methylprednisolone or multiple IM injections of 5 to 15 units per site of botulinum toxin A (Botox(R)) into various tender points on the head identified using algometry. The amount of botulinum toxin A varied with each patient. Visual analog pain scores were assessed at baseline and 30 and 60 days posttreatment for all patients. Quantitative algometry was performed in 5 patients at these same time points. At baseline and 30 days there was no difference in pain severity scores between the 2 groups (p=0.94 and p=0.67, respectively). However, at 60 days posttreatment there was a statistically significant difference in the median visual analog pain scores between the two groups, with the botulinum toxin A group experiencing less pain (p=0.0003). No adverse events were reported.
A study by Smuts et al addressed the use of botulinum toxin A for the prophylaxis of chronic tension-type headache (TTH). Investigators recruited 41 patients meeting the International Headache Society criteria for chronic TTH who had failed prior prophylactic drug therapy. Using a double-blind, placebo-controlled design, patients were randomized to receive either IM injections of 100 units botulinum toxin A (Botox(R)) or an equivalent volume of normal saline. The injections were given in 2 sites in the temporal muscles and 4 sites in the cervical muscles bilaterally. Patients kept a headache diary for 4 weeks prior to treatment, and for 3 months afterwards. Headache pain was recorded using a 6-point scale, and a chronic pain index was used as an indirect quality-of-life measurement. The authors noted a statistically significant improvement in headache pain and headache-free days in the botulinum toxin A group compared with baseline values after 3 months. The botulinum toxin A group also experienced a statistically significant improvement in chronic pain index scores from baseline by month 3 (p=0.001). No between-group differences were noted with respect to adverse effects.

Support for using Botox to treat thoracic outlet syndrome can be found in a study by Jordan et al. Chemodenervation of the scalene muscles using botulinum toxin injections has been associated with substantial relief of symptoms related to thoracic outlet syndrome. In a study of 22 patients unresponsive to physical therapy and suboptimally managed with anesthetic and steroid injections, botulinum toxin 100 units was administered, under electrophysiologic and fluoroscopic guidance (12 units each into the anterior and middle scalene muscles, 76 units into the ipsilateral trapezius muscle). During a 6-month follow-up period, 14 of 22 (64%) patients reported greater than 50% relief of pain, numbness, and fatigue of the treated upper

extremity. This improvement lasted for an average of 88 days (range 30 to 180 days). In contrast, only 4 of 22 patients responded similarly following lidocaine and steroid injections (p=0.0051). The positive, long-lasting response associated with botulinum toxin is useful for patients awaiting surgical decompression for this disorder.

Support for using Botox to treat whiplash injury to neck can be found in a study by Freund and Schwartz. Botulinum A toxin (Botox(R)) as a total of 100 units injected into five tender cervical muscle trigger points decreased subjective neck pain with resultant increase in range of motion but had only equivocal effects on functioning in a randomized, double-blind, placebo-controlled trial (n=26). Subjects had chronic whiplash-associated neck pain following a motor vehicle accident that occurred an average of 3 years prior to baseline. At 4 weeks post-injection, the composite visual analogue scale (VAS) score for neck pain, headache and shoulder pain was significantly lower and total range of neck motion was significantly greater in the botulinum group as compared with the saline group (p less than 0.01). However, the Vernon-Mior score revealed no statistical difference in subjective functioning. Botulinum A toxin did not induce adverse effects.

Support for using Dysport to treat achalasia in a patient who is not a surgical candidate can be found in a study by Mikaeli et al. There was no significant difference between adjunctive treatment with abobotulinumtoxinA before pneumatic dilatation compared with pneumatic dilatation alone for the treatment of newly diagnosed achalasia in a prospective, randomized, controlled trial (n=52). Adults (18 years (yr) or older) with symptomatic, treatment-naïve achalasia were eligible and enrolled consecutively. Patients with functional class 3 or 4 cardiovascular disability and coagulopathy were excluded. Patients were randomly assigned to receive two 50-unit aliquots (0.5 milliliters) of abobotulinumtoxinA (400 units total dose) injections to each quadrant of the lower esophageal sphincter 1 month before pneumatic dilatation (PD) (n=26; median age 38 yr; interquartile range (IQR), 26 to 49 yr; 62% male) or PD-alone (n=26; median age 30 yr; IQR, 24 to 45 yr; 46% male). PD was performed with a 30 millimeter (mm) balloon, gradually inflated up to 10 pounds per square inch in 30 seconds (sec) and maintained for another 60 sec for all patients. Clinical evaluation was performed at baseline, 1-month after treatment, and every 6 months thereafter for 1 year. Clinical response was defined as a symptomatic total score less than 4 and relapse was defined as a symptomatic total score of 4 or greater. The symptomatic total score was based on 5 symptoms: dysphagia with solids, dysphagia with liquids, and active regurgitation, ranked as 0=none, 1=weekly, 2=daily and 3=with each meal, and passive regurgitation and chest pain, ranked as 0=none, 1=monthly, 2=weekly, and 3=daily. Despite significant reductions in total symptom scores within treatment groups at 1 month, which were sustained at 12 months (p less than 0.001), the cumulative remission (response) rate at 12 months was not significantly different between treatment groups. At 12 months, after a single treatment with abobotulinumtoxinA before PD, the cumulative remission rate was 77% (95% CI, 68% to 86%) compared with 62% (95% CI, 52% to 72%; p log rank=0.1) with PD-alone. Relapse occurred in 23% (6/26) of evaluable patients in the abobotulinumtoxinA before PD group and 38% (10/26) of evaluable patients in the PD-alone group. Relapse patients received a second treatment of PD-alone with a 35 mm balloon. After retreatment, 100% of patients in the abobotulinumtoxinA before PD group and 85% of patients in the PD-alone group had symptomatic remission at 12 months from initial treatment. The cumulative remission rate was significantly higher in the abobotulinumtoxinA before PD group compared with PD-alone group after retreatment (p less than 0.05). No significant bleeding, perforation or aspiration occurred in either group or no confounding factor was found to be a predictor of treatment response.
Additionally, Kroupa et al (2010) found adjuvant therapy with abobotulinumtoxinA prior to pneumatic dilatation did not offer additional benefit compared with pneumatic dilatation alone for the treatment of esophageal achalasia in a prospective, historical-controlled study (n=91). Treatment-experienced and -naive adults with achalasia who underwent combined treatment (n=51; mean age 49.7 years (yr); range 24 to 83 yr; 39% male) were compared with historical controls who received PD-alone using the same procedural method and time protocol for evaluation (n=40; age range 26 to 80 yr; 40% male). Prior interventions among treatment-experienced patients included pharmacological treatment with nitrates or nifedipine (46/51), surgical myotomy (3/51), and at least 1 pneumatic dilatation (6/51) Eight days prior to pneumatic dilatation (PD), the adjuvant-therapy group received abobotulinumtoxinA 200 international units (IU) total dose injected in 0.5 milliliter aliquots in the z-line area of each quadrant of the lower esophageal sphincter (LES). PD was performed with a 30 millimeter (mm) balloon for dilatation 1, and a 35 mm balloon for subsequent dilatations. Repeat dilatations were indicated for patients with insufficient cardia relaxation after dilatation 1 as evident upon X-ray verification. Follow-up was conducted every 3 months (mo) for the first year, then annually thereafter; with a mean follow-up duration of 48 mo (range, 12 to 96 mo) and 42 mo (range, 12 to 96 mo) in the adjuvant therapy and control groups, respectively. Efficacy was assessed by application of a grading scale (1=excellent to 5=failure/complete relapse) for symptoms of dysphagia with liquids and solids, heartburn, regurgitation, chest

pain or pressure, and weight change. Remission was defined as no or mild dysphagia, and acceptable individual symptoms as compared with baseline levels. About 3 to 4 days following the initial PD, 13 patients required 2 dilatations and 4 patients required 3 dilatations. For the adjuvant-therapy group, baseline measurements were 4.6 points (95% CI, 3.8 to 5.4 points) and 29 mmHg (range, 10 to 80 mmHg) for mean symptom score and median LES pressure, respectively. The initial treatment effect was observed in 91% (43/47) of patients (4 patients were lost to follow-up). After 3 months, the mean symptom score improved to 2.1 points (95% CI, 0.8 to 3.4 points) and the median LES pressure significantly improved to 14 mmHg (range, 5 to 26 mmHg; p less than 0.001). However, LES pressure slightly increased to 17 mmHg (range 8 to 40 mmHg) and 19 mmHg (9 to 38 mmHg) after 2 and 5 yr since initial treatment, respectively. Treatment durability was sustained in 75% (31/41) of patients with greater than 2-yr follow-up, and 70% (12/17) of patients with greater than 5 yr follow-up. The cumulative remission rate at the end of 5 yr was not significantly different between the adjuvant-therapy group (69%; 95% CI, 61% to 77%) and the historical control groups 50% (95% CI, 41% to 59%; p=0.07). Of 17% (8/47) of patients with relapse dysphagia, laparoscopic Heller myotomy was performed without complications. The most common adverse event was heartburn (36%), which was treated with proton pump inhibitors.

Support for using Dysport to treat blepharospasm can be found in a study by Truong et al. In a multicenter, phase 2, randomized, double-blind, placebo-controlled, parallel-group trial (n=120), a single injection of abobotulinumtoxinA 40 units, 80 units, or 120 units per eye was superior to placebo for the treatment of benign essential blepharospasm (BEB). Adults (age range, 33 to 91 years (yr)) with bilateral BEB for at least 6 months and who scored at least 8 points on the Blepharospasm Disability Scale (BDS; range, 0 to 26 points; higher score indicates greater disability) were eligible. Receipt of botulinum toxin prior to study entry was allowed provided a minimum of 12 weeks had elapsed since the last injection. Use of concomitant medications (e.g., benzodiazepines) that could potentially compromise evaluation of study outcomes was not permitted; however, concomitant use of antispasmodics, muscle relaxants, or other medications affecting the neuromuscular junction was allowed provided doses were stable during the study period. Patients were randomized to receive a total dose per eye of either abobotulinumtoxinA 40 units (n=30; median age, 66 yr; 68% female), 80 units (n=31; median age, 67 yr; 77% female), 120 units (n=31; median age, 62 yr; 81% female) or placebo (n=28; median age 62 yr; 68% female) injected subcutaneously in 0.1 milliliter (mL) aliquots into 6 areas of the orbicularis oculi muscle (0.6 mL total volume/eye). The primary outcome was improvement in functional disability, measured as the difference in the median percentage of normal activity on the BDS between active treatment and placebo at week 4. Notably, 50% of patients in placebo group dropped out of the study citing lack of efficacy compared with 20%, 16%, and 10% of patients in the abobotulinumtoxinA 40-, 80-, and 120-unit dose groups, respectively. An intent-to-treat analysis at week 4 showed significant improvement in functional disability with all abobotulinumtoxinA doses compared with placebo (p less than 0.01); improvement was dose-related and was sustained through week 12. Among secondary outcomes, the frequency of involuntary movements (FIM; measured using a modified FIM scale; range, 0 (no involuntary movements) to 5 (movements present greater than 75% of the time)) and the severity of oculofacial spasm (measured using the Severity Rating Scale) significantly improved at weeks 4, 8, and 12 with all doses of abobotulinumtoxinA compared with placebo. Median differences over placebo in FIM scores at week 4 were -2 (95% confidence interval (CI), -3 to -1), -3 (95% CI, -4 to -2), and -3 (95% CI, -4 to -1) for the 40-unit, 80-unit, and 120-unit dose groups, respectively (p less than 0.001 for all); correspondingly, median differences over placebo in the severity of oculofacial spasm scores were -1 (95% CI, -2 to -1), -2 (95% CI, -2 to -1) and -2 (95% CI, -2 to -1), respectively (p less than 0.001 for all). Improvements in the primary and secondary outcomes were maintained through week 16 only in the 80- and 120-unit groups (p less than 0.05). AbobotulinumtoxinA was well tolerated, with dose-related treatment events that were mild to moderate in severity and resolved without sequelae. Common events included eyelid ptosis, blurred vision, lagophthalmos, diplopia, increased lacrimation, and aggravated dry eyes.

Support for using Dysport to treat hemifacial spasm can be found in a study by Jitpimolmard, Tiamkao, and Laopaiboon. The authors conducted a long-term, prospective, descriptive study (n=158), serial abobotulinumtoxinA injections were effective and led to sustained improvement of hemifacial spasm in adults. Over a 7-year period, 175 consecutive patients with idiopathic hemifacial spasm received abobotulinumtoxinA subcutaneous injections, with the dose ranging from 28 to 220 units per treatment session based on sites and severity of the spasm. The primary injection sites were the medial and lateral lower eyelid; and the lateral junction area of the orbital and preseptal orbicularis oculi, below the lateral eyebrow and orbital area of the upper eyelid. The upper eyelid injection site was later shifted to the lateral orbital orbicularis oculi above the lateral eyebrow to reduce the incidence of ptosis. Subsequent injections were administered upon recurrence of spasm and if patient perception of the spasm was severe enough to request additional treatment. Efficacy

assessments, which included peak improvement (measured using a visual analog scale; range, 0% to 100%) and duration of improvement, were conducted for 855 treatments administered to 158 patients (mean age, 49.1 +/- 11.39 years; 75% female). The median number of treatments was 4 (range, 1 to 19) and the mean follow-up period was 2.39 years (range, 3 to 80 months). The median duration of hemifacial spasm prior to receiving treatment was 4 years (range, 0.25 to 25 years). Among the 855 treatments, the response rate was 97%, with an adjusted mean peak improvement of 77.2% (95% confidence interval (CI), 74.7% to 79.4%); 70% of the treatments were rated as 75% to 100% improved. The adjusted duration of improvement was 3.4 months (95% CI, 3.2 to 3.6 months). Analysis of serial injections from treatment 1 up to treatment 12 revealed sustained effects for mean peak improvement (range, 72.07% to 80.17%) and duration of improvement (range, 2.93 to 3.71 months), but there was no additional benefit in either parameter over the series of treatments (p=0.4 and p=0.87, respectively). Of 26 treatment failures (peak improvement of less than 20%) occurring in 23 patients, subsequent treatments at the same dose (n=12) or higher dose (n=6) resulted in satisfactory improvements. Over 855 treatments, the most common adverse events were ptosis (22.1%) and drooping of the mouth (8.38%). Ptosis resolved in a mean of 2.64 weeks (range, 1 to 4 weeks). Following the change in site of upper eyelid administration, the incidence of ptosis significantly reduced from 27.17% (138 treatments) to 9.67% (21 treatments; p less than 0.001), with no significant difference in mean peak improvement or duration of improvement.

Support for using Myobloc to treat axillary hyperhidrosis can be found in a study by Hecht, Birklein, and Winterholler. Botulinum toxin type B effectively treated axillary hyperhidrosis in 4 patients. Patients received 250 mouse units (diluted in 2.5 milliliters saline) of botulinum toxin type B injected subcutaneously into 10 to 15 sites in each axilla. Using gravimetry, the mean pretreatment axillary sweating was 212.5 milligrams (mg) and 161.3 mg on the right and left sides, respectively. Three weeks after the botulinum toxin type B injections, 3 of 4 patients had axillary anhidrosis. In the other patient axillary sweating had decreased from 585 mg on the right side and 408 mg on the left side to 27 mg and 10 mg on the right and left sides, respectively. The effect duration ranged from 1 to 3 months. No adverse effects were reported.

Support for using Myobloc to treat bladder muscle dysfunction leading to overactive bladder can be found in a study by Dykstra, Enriquez, and Valley. The results of a prospective, open-label, dose-escalation study suggest that botulinum toxin type B (Myobloc(R)) is effective for overactive bladder and the effect duration may be dose related. All patients (n=15) were female, had symptoms of overactive bladder for at least 6 months, and urinary frequency of 8 or more micturitions per 24 hours with or without incontinence. Botulinum toxin type B was injected into the bladder wall at 10 different sites (trigone was avoided) at doses of 2500 Units (n=5), 3750 Units (n=4), 5000 Units (n=2), 10,000 Units (n=2), or 15,000 Units (n=3). Fourteen of 15 patients responded to treatment with decreased frequency, urgency, and no incontinence; the average decrease in the number of frequency episodes per day was 5.27 (p less than 0.001). There was a correlation between the dosage and the response duration (correlation coefficient=0.96, p less than 0.001). The shortest response duration (approximately 3 weeks) occurred at the 2500 Unit dose while the longest response duration (approximately 3 months) occurred in the patients who received 10,000 Unit and 15,000 Unit doses. Five patients experienced mild, transient injection site discomfort and 2 patients in the 15,000 Unit group reported mild general malaise and dry mouth.

Support for using Myobloc to treat bladder spasticity to a spinal cord injury can be found in a publication by Pistolesi et al. In a case report, botulinum toxin type B (NeuroBloc(R)) effectively treated bladder spasticity in a spinal cord injury patient with demonstrated resistance to botulinum toxin type A. The patient received an injection of 5000 International Units of botulinum toxin type B at 20 detrusor muscle sites (the trigone was spared). Four days after injection, the patient was continent and had increased bladder capacity. One month postinjection, the increased bladder capacity persisted and the maximum detrusor pressure had decreased. Dry mouth and dry eyes were the only reported adverse events, which resolved by day 20.

Support for using Myobloc to treat blepharospasm and hemifacial spasm can be found in the American Hospital Formulary System- Drug Information resource. Myobloc has been used in the management of blepharospasm. The available published studies are in patients who have responded previously to onabotulinumtoxinA. The American Academy of Neurology (AAN) states that onabotulinumtoxinA and incobotulinumtoxinA should be considered as treatment options, and abobotulinumtoxinA may be considered for the treatment, of blepharospasm; AAN does not make a recommendation regarding rimabotulinumtoxinB for this use due to lack of data (Simpson, 2016).

Support for using Myobloc to treat palmar hyperhidrosis can be found in a study by Baumann et al. Twenty participants (10 men, 10 women) diagnosed with palmar hyperhidrosis were injected with either Myobloc (5,000 U per palm) or a 1.0 mL vehicle (100 mM NaCl, 10 mM succinate, and 0.5 mg/mL human albumin) into bilateral palms (15 Myobloc, 5 placebo). The participants were followed until sweating returned to baseline levels. The main outcome measures were safety, efficacy versus placebo, and duration of effect. A significant difference was found in treatment response at day 30, as determined by participant assessments, between 15 participants injected with Myobloc and 3 participants injected with placebo. The duration of action, calculated in the 17 participants who received Myobloc injections and completed the study, ranged from 2.3 to 4.9 months, with a mean duration of 3.8 months. The single most reported adverse event was dry mouth or throat, which was reported by 18 of 20 participants. The adverse event profile also included indigestion or heartburn (60%), excessively dry hands (60%), muscle weakness (60%), and decreased grip strength (50%). Myobloc proved to be efficacious for the treatment of palmar hyperhidrosis. Myobloc had a rapid onset, with most participants responding within 1 week. The duration of action ranged from 2.3 to 4.9 months, with a mean of 3.8 months. The adverse event profile included dry mouth, indigestion or heartburn, excessively dry hands, muscle weakness, and decreased grip strength.

Support for using Myobloc to treat spastic dysphonia can be found in a case report by Sataloff et al. Botulinum toxin type B was an effective treatment for spasmodic dysphonia for a patient who had developed resistance to botulinum toxin type A. The 49-year-old patient received an injection of 750 mouse units of botulinum toxin type B in the left thyroarytenoid muscle and 500 mouse units of botulinum toxin type B in the right thyroarytenoid muscle. Improvement was reported 8 days after the injection; the response lasted approximately 14 weeks.

Support for using Myobloc to treat upper limb spasticity can be found in a study by Brashear et al. The authors conducted a double-blind, placebo-controlled, randomized trial. 10,000 units of botulinum toxin type B was administered over a 16-week treatment period was not found to be beneficial in lowering muscle tone in the elbow, wrist, or finger flexors when compared to placebo of post-stroke patients. However, in the open-label portion of the trial, Botulinum toxin type B at four weeks showed statistically significant improvements in muscle tone in the elbow (p=0.039), wrist (p=0.002), finger (p=0.001), and thumb flexors (p=0.002). Fifteen patients (8 male) were enrolled into the double-blinded trial with ten patients randomized to the botulinum toxin type B arm. Following 16 weeks of therapy, thirteen patients continued into the open-label trial. Efficacy was measured with the 5-point Ashworth Scale, which is designed to measure the degree of spasticity in the muscle. While global assessment of change (GAC) did not reach significance in the double-blind trial, GAC did show statistically significant improvement with botulinum toxin type B in the open-label trial as reported on the physician, patient, and occupational therapist GAC scales. No improvements were seen with regards to function and pain (via a Jebsen test, 9-hole peg test, or pain assessment) in either trial. Overall, botulinum toxin type B produced mild side effects; vital signs were not shown to have changed significantly with treatment. The most commonly reported adverse effect was dry mouth, which occurred in 89% of the treatment group versus 20% of the placebo group. The researchers noted that the high prevalence of dry mouth with botulinum toxin type B treatment could have led to possible unblinding. Ten subjects also experienced dry mouth in the open label trial, but all subjects had complete resolution of dryness by week 12 of the trial. One patient with a history of stroke and atrial fibrillation in the double-blind trial died of a large stroke following his week 4 follow-up visit; this serious adverse effect did not appear to be related to botulinum toxin type B. The authors conclude small sample size may have accounted for why the primary endpoint was not found to be statistically significant in the double-blinded trial, and that the disparity in results between the double-blind and open-label study may have resulted from rater bias.

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BREYANZI (lisocabtagene maraleucel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Breyanzi is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) (including DLBCL arising from indolent lymphoma), high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B who have:
1. Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
2. Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
3. Relapsed or refractory disease after two or more lines of systemic therapy

Limitations of use: Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma.

B. Compendial Uses
1. Human immunodeficiency virus(HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
2. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
3. Pediatric primary mediastinal large B-cell lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Primary central nervous system lymphoma
B. Previous treatment course with the requested medication or another CD19-directed chimeric antigen receptor (CAR) T-cell therapy.
C. ECOG performance status greater than or equal to 3 (member is not ambulatory and not capable of all self-care, confined to bed or chair more than 50% of waking hours)
D. Inadequate and unstable kidney, liver or cardiac function
E. Active hepatitis B, active hepatitis C or any active uncontrolled infection
F. Active graft versus host disease
G. Active inflammatory disorder

III. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Chart notes, medical record documentation or claims history supporting previous lines of therapy.

IV. CRITERIA FOR INITIAL APPROVAL

A. Adult Large B-cell Lymphomas

Authorization of 3 months may be granted for treatment of B-cell lymphomas in members 18 years of age or older when either of the following criteria are met:

1. The member has received prior treatment with two or more lines of systemic therapy and has any of the following B-cell lymphoma subtypes:
    i. Diffuse large B-cell lymphoma (DLBCL) [including DLBCL not otherwise specified (NOS), follicular lymphoma grade 3, DLBCL arising from indolent lymphomas]
    ii. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma NOS)
    iii. Primary mediastinal large B-cell lymphoma
    iv. HIV-related B-cell lymphomas (including HIV-related DLBCL, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma NOS)
    v. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
2. The member has received prior treatment with first-line chemoimmunotherapy and has any of the following B-cell lymphoma subtypes:
    i. Diffuse large B-cell lymphoma (DLBCL) [including DLBCL not otherwise specified (NOS), follicular lymphoma grade 3, DLBCL arising from indolent lymphomas]
    ii. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma NOS)
    iii. Primary mediastinal large B-cell lymphoma
    iv. HIV-related B-cell lymphomas (including HIV-related DLBCL, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma NOS)
    v. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)

B. Pediatric Primary Mediastinal Large B-cell Lymphoma

Authorization of 3 months may be granted for treatment of primary mediastinal large B-cell lymphoma in members less than 18 years of age when the member has received prior therapy with at least two prior chemoimmunotherapy regimens and achieved partial response

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Breyanzi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-cell Lymphomas
4. NCCN Guideline: Pediatric aggressive mature B-cell lymphomas
5. National Coverage Determination: Chimeric Antigen Receptor (CAR) T-cell Therapy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Breyanzi are covered in addition to the following:

1. Human immunodeficiency virus(HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
2. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
3. Pediatric primary mediastinal large B-cell lymphoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Breyanzi to treat human immunodeficiency virus (HIV)-related B-cell lymphomas, pediatric primary mediastinal large B-cell lymphoma, and monomorphic post-transplant lymphoproliferative disorder can

be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

All FDA and compendial indications are covered according to the conditions outlined in National Coverage Determination Manual section 110.24 (Chimeric Antigen Receptor [CAR] T-cell Therapy).

VII. REFERENCES

1. Breyanzi [package insert]. Bothell, WA: Juno Therapeutics Inc.; July 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 13, 2023.
3. The NCCN Clinical Practice Guidelines in Oncology® B-Cell Lymphomas (Version 2.2023). © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 13, 2023.
4. National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24-Version 1). https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=374&ncdver=1&DocID=110.24&SearchType=Advanced&bc=EAAAAAIAAAAA&. Accessed April 17, 2023.

BRIUMVI (ublituximab-xiiy)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Briumvi is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Relapsing forms of multiple sclerosis
Authorization of 12 months may be granted to members who have been diagnosed with a relapsing form of multiple sclerosis (including relapsing-remitting and secondary progressive disease for those who continue to experience relapse).

B. Clinically isolated syndrome
Authorization of 12 months may be granted to members for the treatment of clinically isolated syndrome of multiple sclerosis.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Briumvi.
B. Briumvi is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Briumvi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Briumvi are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Briumvi [package insert]. Morrisville, NC: TG Therapeutics, Inc.; December 2022.

CAMCEVI (leuprolide mesylate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Camcevi is indicated for the treatment of adult patients with advanced prostate cancer.

B. Compendial Use
Prostate Cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Prostate Cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced an unacceptable toxicity.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Camcevi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Prostate cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Camcevi are covered in addition to several other treatment settings for prostate cancer.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Camcevi for treating prostate cancer, including the FDA-approved indication of advanced prostate cancer, can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Camcevi [package insert]. Durham, NC: Accord BioPharma Inc.; May 2021.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed February 1, 2023.

CARVYKTI (ciltacabtagene autoleucel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Carvykti is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Chart notes, medical record documentation or claims history supporting previous lines of therapy

III. CRITERIA FOR INITIAL APPROVAL

Multiple Myeloma
Authorization of 3 months may be granted for treatment of relapsed or refractory multiple myeloma in members 18 years of age and older when all of the following criteria are met:

A. The member has received prior treatment with at least four prior lines of therapy, including at least one drug from each of the following categories:
    1. Immunomodulatory agent
    2. Proteasome inhibitor
    3. Anti-CD38 monoclonal antibody
B. The member has not received previous treatment with the requested medication or another CAR-T therapy directed at any target.
C. The member has an ECOG performance status of 0 to 2.
D. The member has adequate and stable kidney, liver, pulmonary and cardiac function.
E. The member does not have known active or prior history of central nervous system (CNS) involvement, including CNS multiple myeloma.
F. The member does not have clinically significant active infection.
G. The member does not have active graft versus host disease.
H. The member does not have an active inflammatory disorder.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Carvykti.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Multiple myeloma

4. National Coverage Determination: Chimeric Antigen Receptor (CAR) T-cell Therapy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Carvykti are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

All FDA-approved indications are covered according to the conditions outlined in National Coverage Determination Manual section 110.24 (Chimeric Antigen Receptor [CAR] T-cell Therapy).

VI. REFERENCES

1. Carvykti [package insert]. Horsham, PA: Janssen Biotech, Inc.; February 2023.
2. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021 Jul 24;398(10297):314-324.
3. National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24-Version 1). https://www.cms.gov/medicare-coverage-database/search.aspx. Accessed October 11, 2023.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Multiple Myeloma. Version 2.2024. Accessed December 14, 2023.
5. Patel U, Oluwole OO, Kassim A, et al. Sequencing bispecific antibodies and CAR T cell therapy in multiple myeloma with prior exposure to BCMA-targeted therapies. *J Clin Oncol*. 2023;41(16):e20049.

CASGEVY (exagamglogene autotemcel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

1. Casgevy is indicated for the treatment of sickle cell disease (SCD) in patients 12 years and older with recurrent vaso-occlusive crises (VOCs).
2. Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years and older.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Sickle cell disease:
   1. Molecular or genetic testing results documenting sickle cell disease genotype
   2. Chart notes or medical records documenting history of severe vaso-occlusive episodes
B. Transfusion-dependent β-thalassemia:
   1. Molecular or genetic testing results documenting transfusion-dependent β-thalassemia genotype
   2. Chart notes or medical records documenting history of blood cell transfusions

III. CRITERIA FOR INITIAL APPROVAL

A. Sickle Cell Disease

Authorization of one dose total may be granted for sickle cell disease when all of the following criteria are met:

1. Member is 12 years of age or older.
2. Member has a diagnosis of sickle cell disease with one of the following genotypes confirmed by molecular or genetic testing:
   a. β^s/β^s
   b. β^s/β^0
   c. β^s/β^+
3. Member has a documented history of at least 2 severe vaso-occlusive episodes per year during the previous two years (see Appendix A for examples).
4. Member is eligible for a hematopoietic stem cell transplant (HSCT) but is unable to find a human leukocyte antigen (HLA)-matched related donor.
5. Member has not received a prior hematopoietic stem cell transplant (HSCT).
6. Member has not received Casgevy or any other gene therapy previously.

B. Transfusion-Dependent β-Thalassemia

Authorization of one dose total may be granted for transfusion-dependent β-thalassemia when all of the following criteria are met:

1. Member is 12 years of age or older.
2. Member has a diagnosis of transfusion-dependent β-thalassemia with a non-β0/β0 OR β0/β0 genotype confirmed via molecular or genetic testing (see Appendix B for examples).
3. Member has received at least 100 milliliter per kilogram or 10 units of packed red blood cells (pRBCs) per year during the previous two years.

4. Member is eligible for a hematopoietic stem cell transplant (HSCT) but is unable to find a human leukocyte antigen (HLA)-matched related donor.
5. Member has not received a prior hematopoietic stem cell transplant (HSCT).
6. Member has not received Casgevy or any other gene therapy previously.

IV. APPENDIX

A. Examples of Severe Vaso-Occlusive Events
   1. Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
   2. Acute chest syndrome
   3. Priapism lasting > 2 hours and requiring a visit to a medical facility
   4. Splenic sequestration
   5. Hepatic sequestration

B. Examples of non-β0/β0 OR β0/β0 genotypes
   1. β0/β0
   2. β0/β+
   3. βE/β0
   4. β0/IVS-I-110
   5. IVS-I-110/IVS-1-110

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Casgevy.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. National Institutes of Health.
4. 2021 Guidelines for the management of transfusion dependent thalassaemia (TDT).

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Casgevy are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the list of examples of severe vaso-occlusive events can be found in both the clinical trials of Casgevy and Lyfgenia. In addition, the list is further supported by the Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014.

VII. REFERENCES

1. Casgevy [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; January 2024.
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CEREZYME (imiglucerase)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Cerezyme is indicated for treatment of adults and pediatric patients 2 years of age and older with Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, and/or hepatomegaly or splenomegaly.

B. Compendial Uses
1. Gaucher disease type 2
2. Gaucher disease type 3

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For initial requests: beta-glucocerebrosidase enzyme assay or genetic testing results supporting diagnosis.

III. CRITERIA FOR INITIAL APPROVAL

A. Gaucher disease type 1
Authorization of 12 months may be granted for treatment of Gaucher disease type 1 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

B. Gaucher disease type 2
Authorization of 12 months may be granted for treatment of Gaucher disease type 2 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

C. Gaucher disease type 3
Authorization of 12 months may be granted for treatment of Gaucher disease type 3 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.

C. The member is receiving benefit from therapy. Benefit is defined as not experiencing an inadequate response or any intolerable adverse events from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Cerezyme.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Gaucher disease: GeneReviews.
4. Revised recommendations for the management of Gaucher disease in children.
5. Management of neuronopathic Gaucher disease: revised recommendations. European Working Group on Gaucher Disease.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cerezyme are covered in addition to the following:

A. Gaucher disease type 2
B. Gaucher disease type 3

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The diagnosis of Gaucher disease relies on demonstration of deficient glucocerebrosidase (glucosylceramidase) enzyme activity in peripheral blood leukocytes or other nucleated cells or by the identification of biallelic pathogenic variants in *GBA1* (formerly *GBA*). (Pastores and Hughes).

Support for using Cerezyme to treat Gaucher disease type 2 can be found in the National Organization for Rare Disorders Guide to Rare Disorders. Enzyme replacement therapy (ERT) is effective for type 1 disease. Anemia and thrombocytopenia improve, hepatomegaly and splenomegaly are reduced, and skeletal damage is ameliorated with ERT. These systemic manifestations also improve with ERT in patients with type 2 and 3 disease. However, it should be noted that ERT does not reverse brain damage in patients with type 2 disease.

Support for using Cerezyme to treat Gaucher disease type 3 can be found in the Revised Recommendations for the Management of Gaucher Disease by Kaplan et al. The guideline indicates symptomatic children with types 1 or 3 disease should receive enzyme replacement therapy, which will prevent debilitating and often irreversible disease progression and allow those with non-neuropathic disease to lead normal healthy lives.

VII. REFERENCES

1. Cerezyme [package insert]. Cambridge, MA: Genzyme Corporation; December 2022.
2. Altarescu G, Hill S, Wiggs E, et al. The efficacy of enzyme replacement therapy in patients with chronic neuronopathic Gaucher's disease. *J Pediatr.* 2001;138:539-547.
3. Erikson A, Forsberg H, Nilsson M, Astrom M, Mansson JE. Ten years' experience of enzyme infusion therapy of Norrbottnian (type 3) Gaucher disease. *Acta Paediatr*. 2006;95:312-317.
4. Pastores GM, Hughes DA. Gaucher Disease. 2000 July 27 [Updated March 9, 2023]. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2023.
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6. National Organization for Rare Disorders. (2003). NORD guide to rare disorders. Philadelphia: Lippincott Williams & Wilkins.

CIMZIA (certolizumab pegol)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications[1]
1. Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
2. Treatment of adults with moderately to severely active rheumatoid arthritis.
3. Treatment of adult patients with active psoriatic arthritis.
4. Treatment of adults with active ankylosing spondylitis.
5. Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation.
6. Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

B. Compendial Uses[28]
Immune checkpoint inhibitor-related toxicity – inflammatory arthritis

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

Crohn's disease (CD), Rheumatoid arthritis (RA), Psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), plaque psoriasis (PsO), and immune checkpoint inhibitor-related toxicity
For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Crohn's disease (CD)[1]
Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

B. Rheumatoid arthritis (RA)[1]
Authorization of 12 months may be granted for treatment of moderately to severely active rheumatoid arthritis.

C. Psoriatic arthritis (PsA)[1]
Authorization of 12 months may be granted for the treatment of active psoriatic arthritis.

D. Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)[1]
Authorization of 12 months may be granted for treatment of active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

E. Plaque psoriasis (PsO)[1]
Authorization of 12 months may be granted for treatment of moderate to severe plaque psoriasis.

F. Immune checkpoint inhibitor-related toxicity[28]
Authorization of 12 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when the member has severe immunotherapy-related inflammatory arthritis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

All indications
Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Cimzia.
B. Cimzia is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Cimzia.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2016 Update of the international ASAS-EULAR management recommendations for axial spondyloarthritis.
4. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update.
5. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.
6. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.
7. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions.
8. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies; 2019 update.
9. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021.
10. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis.
11. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis.
12. An evidence-based systematic review on medical therapies for inflammatory bowel disease.
13. ACG Clinical Guideline: Management of Crohn's Disease in Adults.
14. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics.
15. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis.
16. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis in pediatric patients.
17. Joint AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologic therapies.
18. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.
19. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease.
20. Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapy and Alternative Medicine Modalities for Psoriasis Severity Measures.
21. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cimzia are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

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2. van der Heijde D, Ramiro S, Landewe R, et al. 2016 Update of the international ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis.* 2017;0:1-14.
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26. Clinical Consult: CVS Caremark Clinical Programs Review. Focus on Rheumatology Clinical Programs. November 2022.
27. Clinical Consult: CVS Caremark Clinical Programs Review. Focus on Gastroenterology (GI) – Inflammatory Bowel Disease (IBD). April/May 2023.
28. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 10, 2023.

CINQAIR (reslizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Cinqair is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype.

Limitations of Use: Not for relief of acute bronchospasm or status asthmaticus

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests:
    1. Member's chart notes or medical record showing pretreatment blood eosinophil count, dependance on inhaled corticosteroids if applicable.
    2. Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration.
B. For continuation requests: Chart notes or medical record documentation supporting improvement in asthma control.

III. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted for treatment of eosinophilic asthma when all of the following criteria are met:
A. Member is 18 years of age or older.
B. Member has a baseline (pretreatment with a biologic indicated for asthma) blood eosinophil count of at least 400 cells per microliter.
C. Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
    1. Inhaled corticosteroid
    2. Additional controller (i.e., long acting beta$_2$-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline)
D. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Dupixent, Fasenra, Nucala, Tezspire, or Xolair).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months may be granted when all of the following criteria are met:
A. Member is 18 years of age or older.
B. The member is currently receiving therapy with the requested medication.

C. The requested medication is being used to treat an indication enumerated in Section III.
D. The member is receiving benefit from therapy as defined by a reduction in the frequency and/or severity of symptoms and exacerbations.
E. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Dupixent, Fasenra, Nucala, Tezspire, or Xolair).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Cinqair.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2022 update.
4. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cinqair are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Cinqair to treat severe asthma can be found in the Global Initiative for Asthma (GINA) guidelines. For adults, add-on interleukin-5 antagonists can be a drug used when either medium dose maintenance inhaled corticosteroids with formoterol or medium to high dose maintenance inhaled corticosteroids with long-acting beta2-agonists are not controlling the patient's asthma.

VII. REFERENCES

1. Cinqair [package insert]. West Chester, PA: Teva Respiratory, LLC; February 2020.
2. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355-366.
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2022 update. Available at: https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf. Accessed March 1, 2023.
4. Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. *JAMA*. 2020;324(22): 2301-2317.

CINRYZE (C1 esterase inhibitor [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Cinryze is indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years of age and older) with hereditary angioedema (HAE).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial authorization:
   1. C1 inhibitor functional and antigenic protein levels
   2. F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
   3. Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
B. For continuation of therapy, chart notes demonstrating a reduction in frequency of attacks

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

IV. CRITERIA FOR INITIAL APPROVAL

Hereditary angioedema (HAE)
Authorization of 6 months may be granted for prevention of HAE attacks when either of the following criteria is met at the time of diagnosis:
A. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
   1. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
   2. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
B. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
   1. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
   2. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for prevention of HAE attacks when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The member is receiving benefit from therapy. Benefit is defined as:
    1. A significant reduction in frequency of attacks (e.g., ≥ 50%) since starting treatment, and
    2. A reduction in the use of medications to treat acute attacks since starting treatment.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Cinryze.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.
4. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
5. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
6. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.
7. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
8. International consensus on hereditary and acquired angioedema.
9. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.
10. Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.
11. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency.
12. Diagnosis and screening of patients with hereditary angioedema in primary care.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cinryze are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.
When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an

interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

VIII. REFERENCES

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13. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update. Allergy. 2022 Jan 10. doi: 10.1111/all. 15214. Online ahead of print.
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COAGADEX (coagulation factor X [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Coagadex is indicated in adults and children with hereditary Factor X deficiency for:
A. Routine prophylaxis to reduce the frequency of bleeding episodes
B. On-demand treatment and control of bleeding episodes
C. Perioperative management of bleeding in patients with mild, moderate, and severe hereditary Factor X deficiency.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Hereditary Factor X Deficiency
A. Authorization of 12 months may be granted for treatment of hereditary Factor X deficiency when used in either of the following settings:
   1. Prophylaxis to reduce the frequency of bleeding episodes
   2. On-demand treatment and control of bleeding episodes
B. Authorization of 1 month may be granted for perioperative management of bleeding in members with mild, moderate, or severe hereditary Factor X deficiency.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Perioperative management of bleeding
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. All other indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Coagadex.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology

3. MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.
4. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Coagadex are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Coagadex [package insert]. Durham, NC: Bio Products Laboratory USA, Inc.; April 2023.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-280-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-selected-disorders-of-the-coagulation-system. Accessed October 4, 2023.
3. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167(3):304-26.
4. Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. *Haemophilia.* 2008;14(6):1176-82.

COLUMVI (glofitamab-gxbm)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Columvi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.

B. Compendial Uses
B-Cell Lymphomas
1. Diffuse Large B-Cell Lymphoma
2. High Grade B-Cell Lymphoma
3. Histologic Transformation of Indolent Lymphoma to Diffuse Large B-Cell Lymphoma
4. Human Immunodeficiency Virus (HIV)-Related B-Cell Lymphoma
    a. HIV- Related Diffuse Large B-cell Lymphoma
    b. Primary Effusion Lymphoma
    c. Human Herpes Virus Type 8 (HHV8)-Positive Diffuse Large B-cell Lymphoma
5. Monomorphic Post-Transplant Lymphoproliferative Disorder

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

B-cell Lymphoma
Authorization of 12 months may be granted for treatment of B-cell lymphoma after at least 2 prior lines of systemic therapy when the member has partial response, no response, progressive, relapsed or refractory disease and both of the following criteria are met:
1. The member has any of the following subtypes
    A. Diffuse Large B-Cell Lymphoma (DLBCL)
    B. High Grade B-Cell Lymphoma as a single agent
    C. Histologic Transformation of Indolent Lymphoma to DLBCL
    D. HIV-Related B-Cell Lymphoma including HIV-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL, not otherwise specified as a single agent
    E. Monomorphic Post-Transplant Lymphoproliferative Disorder as a single agent
2. The member will be pretreated with a single dose of obinutuzumab (Gazyva) 7 days before initiation with the requested medication.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months (up to a maximum of 12 cycles) may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II

3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Columvi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Columvi are covered in addition to the following:

1. Diffuse Large B-Cell Lymphoma
2. High Grade B-Cell Lymphoma
3. Histologic Transformation of Indolent Lymphoma to Diffuse Large B-Cell Lymphoma
4. Human Immunodeficiency Virus (HIV)-Related B-Cell Lymphoma
    a. HIV- Related Diffuse Large B-cell Lymphoma
    b. Primary Effusion Lymphoma
    c. Human Herpes Virus Type 8 (HHV8)-Positive Diffuse Large B-cell Lymphoma
5. Monomorphic Post-Transplant Lymphoproliferative Disorder

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Columvi to treat all indications listed in section IV can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Columvi [package insert]. South San Francisco, CA: Genentech, Inc.; June 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed July 10, 2023.

CORIFACT (factor XIII concentrate [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Corifact is indicated in adult and pediatric patients with congenital Factor XIII deficiency for routine prophylactic treatment and peri-operative management of surgical bleeding.

B. Compendial Use
Acquired factor XIII deficiency

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Factor XIII Deficiency
Authorization of 12 months may be granted for treatment of factor XIII deficiency.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds)

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Corifact.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.
4. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Corifact are covered in addition to acquired factor XIII deficiency.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Corifact to treat acquired factor XIII deficiency can be found in the Guideline for the Diagnosis and Management of Rare Coagulation Disorders published by the United Kingdom Haemophilia Centre Doctors' Organization. Acquired factor XIII deficiency has been reported in patients with cardiac surgery, inflammatory bowel disease and Henoch-Schonlein purpura and is rarely associated with de novo FXIII inhibitors. Corifact is listed as an appropriate treatment for acquired factor XIII deficiency, which follows the same recommendations as congenital factor XIII deficiency.

VI. REFERENCES

1. Corifact [package insert]. Kankakee, IL: CSL Behring LLC; September 2020.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-280-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-selected-disorders-of-the-coagulation-system. Accessed October 4, 2023.
3. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167(3):304-26.
4. AHFS DI (Adult and Pediatric) [database online]. Bethesda, MD. American Society of Health System Pharmacists, Inc. Electronic version. Updated April 21, 2023. Available with subscription. URL: http://online.lexi.com/lco. Accessed October 4, 2023.

COSELA (trilaciclib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

B. Compendial Use
Prophylaxis of chemotherapy-induced anemia

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Extensive-stage Small Cell Lung Cancer
Authorization of 6 months may be granted to decrease the incidence of chemotherapy-induced myelosuppression or anemia and red blood cell transfusions in adult patients with extensive-stage small cell lung cancer when all of the following criteria are met:
A. The member will be receiving either of the following chemotherapeutic regimens:
   1. A platinum/etoposide-containing regimen.
   2. A topotecan-containing regimen.
B. The requested medication will be given within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Cosela.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Hematopoietic growth factors

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cosela are covered as well as prophylaxis of chemotherapy-induced anemia in patients who will receive a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Cosela to decrease the incidence of anemia from chemotherapy can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors. The NCCN Guideline supports the use of Cosela as a prophylactic option to decrease the incidence of anemia and red blood cell transfusions when administered before platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

VI. REFERENCES

1. Cosela [package insert]. Durham, NC: G1 Therapeutics, Inc; August 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed January 3, 2024.

COSENTYX IV (secukinumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this policy is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

A. FDA-Approved Indications
   1. Adults with active psoriatic arthritis (PsA)
   2. Adults with active ankylosing spondylitis (AS)
   3. Adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation

   The following indications are FDA-approved but the drug approved to treat the indication is usually self-administered and thus not covered by this policy.
   1. Moderate to severe plaque psoriasis (PsO) in patients 6 years of age and older who are candidates for systemic therapy or phototherapy
   2. Active enthesitis-related arthritis (ERA) in patients 4 years of age and older
   3. Adults with moderate to severe hidradenitis suppurativa (HS)
   4. Active psoriatic arthritis in pediatric patients 2 years of age and older

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Psoriatic arthritis (PsA)
Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

B. Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)
Authorization of 12 months may be granted for treatment of active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

All indications
Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Cosentyx.
B. Cosentyx is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Cosentyx.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cosentyx are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCE

1. Cosentyx [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2023.

CRYSVITA (burosumab-twza)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Crysvita is indicated for the treatment of:
1. X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.
2. FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. X-linked hypophosphatemia
   1. Initial requests:
      a. Radiographic evidence of rickets or other bone disease attributed to XLH
      b. At least one of the following:
         i. Genetic testing results confirming the member has a PHEX (phosphate regulating gene with homology to endopeptidases located on the X chromosome) mutation
         ii. Genetic testing results confirming a PHEX mutation in a directly related family member with appropriate X-linked inheritance
         iii. Lab test results confirming the member's serum fibroblast growth factor 23 (FGF23) level is above the upper limit of normal or abnormal for the assay
   2. Continuation of therapy requests: documentation (e.g., chart notes, lab test results) of benefit from therapy (e.g., increase or normalization in serum phosphate, improvement in bone and joint pain, reduction in fractures, improvement in skeletal deformities)
B. Tumor induced osteomalacia
   1. Initial requests:
      a. Lab test results confirming the member's serum fibroblast growth factor 23 (FGF23) level is above the upper limit of normal or abnormal for the assay
      b. Fasting serum phosphorus levels less than 2.5 mg/dL
      c. Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) less than 2.5 mg/dL
   2. Continuation of therapy requests: documentation (e.g., chart notes, lab test results) of benefit from therapy (e.g., increase or normalization in serum phosphate, improvement in bone and joint pain, reduction in fractures, improvement in skeletal deformities)

III. CRITERIA FOR INITIAL APPROVAL

A. X-linked hypophosphatemia (XLH)
Authorization of 12 months may be granted for treatment of X-linked hypophosphatemia when both of the following criteria is met:
1. The member meets one of the following:
   a. Genetic testing was conducted to confirm a PHEX mutation in the member.

b. Genetic testing was conducted to confirm a PHEX mutation in a directly related family member with appropriate X-linked inheritance.
c. Member's FGF23 level is above the upper limit of normal or abnormal for the assay.

2. Member has radiographic evidence of rickets or other bone disease attributed to XLH.

B. Tumor-induced osteomalacia (TIO)

Authorization of 12 months may be granted for treatment of tumor-induced osteomalacia (TIO) when the following criteria is met:

1. Member's diagnosis is confirmed by ALL of the following:
   a. FGF23 level is above the upper limit of normal or abnormal for the assay.
   b. Fasting serum phosphorus levels are less than 2.5 mg/dL.
   c. Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) is less than 2.5 mg/dL.
2. Member's disease is associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., increase or normalization in serum phosphate, improvement in bone and joint pain, reduction in fractures, improvement in skeletal deformities).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Crysvita.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Crysvita are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the diagnostic criteria listed above for X-linked phosphatemia can be found in the design of the confirmational trials. To be eligible for inclusion, the diagnosis of XLH must have been supported by confirmation of phosphate regulating gene with homology to endopeptidases located on the X chromosome (PHEX) mutation in the patient or a directly related family member with appropriate X-linked inheritance, or a serum FGF23 level of greater than 30 pg/mL.

Support for the diagnostic criteria listed above for FGF23-related hypophosphatemia in tumor-induced osteomalacia can be found in the design of the confirmational trials. To be eligible for inclusion, the diagnosis of TIO must have been confirmed by a fasting serum phosphorus level less than 2.5 mg/dL, have an FGF23 level greater than or equal to 100 pg/mL, and have a ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) of less than 2.5 mg/dL.

VII. REFERENCES

1. Crysvita [package insert]. Princeton, NJ: Kyowa Kirin, Inc.; March 2023.
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3. NIH. U.S. National Library of Medicine. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT02526160. Accessed October 24, 2018.
4. Dieter, H., Emma, F., Eastwood, D.M., et.al. Clinical Practice Recommendations for the Diagnosis and Management of X-linked Hypophosphataemia. Nature Reviews Nephrology 15, 435-455 (2019).
5. NIH. U.S. National Library of Medicine. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT02304367. Accessed June 30, 2020.
6. Chong WH, Molinolo AA, Chen CC, et.al Tumor-induced Osteomalacia. Endocrine Related Cancer 18:R53-R77 (2011).
7. Fauconnier C, Roy T, Gillerot G, et al. FGF23: Clinical usefulness and analytical evolution. *Clin Biochem.* 2019

CYRAMZA (ramucirumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. **Gastric Cancer**
   Cyramza as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
2. **Non-Small Cell Lung Cancer (NSCLC)**
   a. Cyramza, in combination with erlotinib, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
   b. Cyramza, in combination with docetaxel, is indicated for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.
3. **Colorectal Cancer**
   Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
4. **Hepatocellular Carcinoma**
   Cyramza as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have an alpha fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib.

B. Compendial Uses

1. Esophageal adenocarcinoma
2. Gastric, gastro-esophageal junction (GEJ), esophagogastric junction (EGJ) cancer – not surgical candidates, recurrent disease, in combination with irinotecan with or without fluorouracil
3. Colorectal cancer:
   a. Anal adenocarcinoma and appendiceal adenocarcinoma
   b. Advanced disease
   c. In combination with irinotecan
   d. Adjuvant treatment
4. NSCLC - recurrent, advanced
5. Urothelial carcinoma
6. Mesothelioma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

Submission of the following information must be available, upon request for initial approval: EGFR mutation testing results and alpha fetoprotein (AFP) level results (where applicable).

III. CRITERIA FOR INITIAL APPROVAL

A. Gastric, Gastro-esophageal Junction (GEJ), Esophagogastric Junction (EGJ), and Esophageal Adenocarcinoma

Authorization of 12 months may be granted for treatment of gastric, gastro-esophageal junction (GEJ), esophagogastric junction (EGJ), and esophageal adenocarcinoma for members who are not surgical candidates or who have unresectable locally advanced, recurrent or metastatic disease, when used as subsequent therapy as a single agent, in combination with paclitaxel, or in combination with irinotecan with or without fluorouracil.

B. Non-Small Cell Lung Cancer (NSCLC)

Authorization of 12 months may be granted for treatment of recurrent, advanced or metastatic NSCLC when either of the following criteria is met:

1. Used in combination with docetaxel as subsequent therapy.
2. Used in combination with erlotinib for EGFR exon 19 deletion or exon 21 (L858R) substitution mutation positive disease.

C. Colorectal Cancer (CRC)

Authorization of 12 months may be granted for treatment colorectal cancer if either of the following criteria is met:

1. Used for advanced or metastatic colorectal cancer, including anal adenocarcinoma and appendiceal adenocarcinoma, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil) or irinotecan.
2. Used as adjuvant treatment in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or irinotecan for unresectable metachronous metastases that converted to resectable disease after initial treatment.

D. Hepatocellular Carcinoma (HCC)

Authorization of 12 months may be granted for subsequent treatment of progressive hepatocellular carcinoma as a single agent in patients who have an alpha fetoprotein (AFP) of greater than or equal to 400 ng/mL

E. Urothelial Carcinoma

Authorization of 12 months may be granted for treatment of advanced or metastatic urothelial carcinoma when all of the following criteria is met:

1. Used in combination with docetaxel.
2. Disease progression within 12 months after platinum-containing chemotherapy.

F. Mesothelioma

Authorization of 12 months may be granted for the subsequent treatment of pleural mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when used in combination with gemcitabine.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. NSCLC

Authorization of 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat non-small cell lung cancer
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity or disease progression while on the current regimen, or
    b. Disease is T790M negative and there is no evidence of unacceptable toxicity while on the current regimen

B. All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section III
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen, and
    b. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Cyramza.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Pleural mesothelioma
4. NCCN Guideline: Non-small cell lung cancer
5. NCCN Guideline: Hepatocellular carcinoma
6. NCCN Guideline: Gastric cancer
7. NCCN Guideline: Esophageal and esophagogastric junction cancers
8. NCCN Guideline: Colon cancer
9. NCCN Guideline: Rectal cancer
10. NCCN Guideline: Anal carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cyramza are covered in addition to the following:

1. Esophageal adenocarcinoma
2. Gastric, gastro-esophageal junction (GEJ), esophagogastric junction (EGJ) cancer – not surgical candidates, recurrent disease, in combination with irinotecan with or without fluorouracil
3. Colorectal cancer:
    a. Anal adenocarcinoma and appendiceal adenocarcinoma
    b. Advanced disease
    c. In combination with irinotecan
    d. Adjuvant treatment
4. NSCLC - recurrent, advanced
5. Urothelial carcinoma
6. Mesothelioma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using Cyramza to treat esophageal adenocarcinoma, gastric, GEJ, and EGJ cancers, colorectal cancer, anal adenocarcinoma, appendiceal adenocarcinoma, NSCLC, and mesothelioma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Cyramza to treat urothelial carcinoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Cyramza [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2022.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed January 3, 2024.
3. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed January 3, 2024.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf. Accessed January 3, 2024.

DANYELZA (naxitamab-gqgk)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
DANYELZA is a GD2-binding monoclonal antibody indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

High-risk neuroblastoma
Authorization of 12 months may be granted for treatment of high-risk neuroblastoma when all of the following criteria are met:
1. The member is 1 year of age or older with relapsed or refractory disease in the bone or bone marrow
2. The member has demonstrated any of the following with prior therapy:
   i. Partial response
   ii. Minor response
   iii. Stable disease
3. The requested medication will be used in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF)

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as no evidence of unacceptable toxicity or disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Danyelza.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Danyelza are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Danyelza [package insert]. New York, NY: Y-mAbs Therapeutics, Inc.; November 2020.

DARZALEX (daratumumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Darzalex is indicated for the treatment of adult patients with multiple myeloma:
1. in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
2. in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
3. in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
4. in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
5. in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
6. in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
7. as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

B. Compendial Uses
1. Multiple myeloma
2. Systemic light chain amyloidosis
3. T-cell acute lymphoblastic leukemia (T-ALL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Documentation of testing or laboratory results confirmation t(11:14) translocation, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Multiple Myeloma
1. Authorization of 12 months may be granted for the treatment of multiple myeloma when used in combination with cyclophosphamide, bortezomib, and dexamethasone.

2. Authorization of 12 months may be granted for the treatment of multiple myeloma as primary therapy when any of the following criteria is met:
    a. The member is ineligible for a transplant and the requested medication will be used in combination with either:
        i. Lenalidomide and dexamethasone
        ii. Bortezomib, melphalan, and prednisone

b. The member is eligible for transplant and the requested medication will be used in combination with any of the following:
    i. Bortezomib, thalidomide, and dexamethasone for a maximum of 16 doses
    ii. Bortezomib, lenalidomide, and dexamethasone
    iii. Carfilzomib, lenalidomide, and dexamethasone
    iv. Ixazomib, lenalidomide, and dexamethasone

3. Authorization of 12 months may be granted for the treatment of previously treated multiple myeloma when any of the following criteria is met:
    a. The requested medication will be used in combination with lenalidomide and dexamethasone in members who have received at least one prior therapy
    b. The requested medication will be used in combination with bortezomib and dexamethasone in members who have received at least one prior therapy
    c. The requested medication will be used in combination with carfilzomib and dexamethasone in members who have received at least one prior therapy
    d. The requested medication will be used in combination with pomalidomide and dexamethasone in members who have received at least one prior therapy including a proteasome inhibitor (PI) and an immunomodulatory agent.
    e. The requested medication will be used in combination with selinexor and dexamethasone
    f. The requested medication will be used in combination with venetoclax and dexamethasone for members with documented t(11:14) translocation
    g. The requested medication will be used as a single agent in members who have received at least three prior therapies, including a PI and an immunomodulatory agent
    h. The requested medication will be used as a single agent in members who are double refractory to a PI and an immunomodulatory agent

4. Authorization of 12 months may be granted for maintenance therapy of symptomatic multiple myeloma for transplant candidates when either of the following criteria is met:
    a. The requested medication will be used as single agent
    b. The requested medication will be used in combination with lenalidomide in members who have high risk disease

B. Systemic Light Chain Amyloidosis
Authorization of 12 months may be granted as a single agent for the treatment of systemic light chain amyloidosis.

C. T-Cell Acute Lymphoblastic Leukemia (T-ALL)
Authorization of 12 months may be granted for treatment for relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen or
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Darzalex.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Systemic light chain amyloidosis
4. NCCN Guideline: Multiple myeloma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Darzalex are covered in addition to the following:

1. Multiple myeloma
2. Systemic light chain amyloidosis
3. T-cell acute lymphoblastic leukemia (T-ALL)

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Darzalex to treat multiple myeloma, and systemic light chain amyloidosis, and T-cell acute lymphoblastic leukemia (T-ALL) can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Darzalex to treat relapsed or refractory systemic light chain amyloidosis can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Darzalex [package insert]. Horsham, PA: Janssen Biotech Inc; January 2023.
2. The NCCN Drugs & Biologics Compendium® ©2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed December 19, 2023.
3. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ Accessed: October 2, 2023.

DARZALEX FASPRO (daratumumab and hyaluronidase-fihj)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Darzalex Faspro is indicated for the treatment of adult patients with multiple myeloma:
      a. in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
      b. in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
      c. in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.
      d. in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
      e. in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor.
      f. in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.
      g. as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

   2. Darzalex Faspro is indicated for the treatment of adult patients with newly diagnosed light chain amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone.

B. Compendial Uses
   1. For multiple myeloma, may be used as a single agent or in combination with other systemic therapies where intravenous daratumumab is recommended
   2. Systemic light chain amyloidosis

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Documentation of testing or laboratory results confirmation t(11:14) translocation, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Multiple Myeloma
   1. Authorization of 12 months may be granted for the treatment of multiple myeloma when used in combination with cyclophosphamide, bortezomib, and dexamethasone.

   2. Authorization of 12 months may be granted for the treatment of multiple myeloma as primary therapy when any of the following criteria is met:

a. The member is ineligible for a transplant and the requested medication will be used in combination with either:
   i. Lenalidomide and dexamethasone
   ii. Bortezomib, melphalan, and prednisone
b. The member is eligible for transplant and the requested medication will be used in combination with any of the following:
   i. Bortezomib, thalidomide, and dexamethasone for a maximum of 16 doses
   ii. Bortezomib, lenalidomide, and dexamethasone
   iii. Carfilzomib, lenalidomide, and dexamethasone
   iv. Ixazomib, lenalidomide, and dexamethasone

3. Authorization of 12 months may be granted for the treatment of previously treated multiple myeloma when any of the following criteria is met:
   a. The requested medication will be used in combination with lenalidomide and dexamethasone in members who have received at least one prior therapy
   b. The requested medication will be used in combination with bortezomib and dexamethasone in members who have received at least one prior therapy
   c. The requested medication will be used in combination with carfilzomib and dexamethasone in members who have received at least one prior therapy
   d. The requested medication will be used in combination with pomalidomide and dexamethasone in members who have received at least one prior therapy including a proteasome inhibitor (PI) and an immunomodulatory agent
   e. The requested medication will be used in combination with selinexor and dexamethasone
   f. The requested medication will be used in combination with venetoclax and dexamethasone for members with documented t(11:14) translocation
   g. The requested medication will be used as a single agent in members who have received at least three prior therapies, including a PI and an immunomodulatory agent
   h. The requested medication will be used as a single agent in members who are double refractory to a PI and an immunomodulatory agent

4. Authorization of 12 months may be granted for maintenance therapy of symptomatic multiple myeloma for transplant candidates when either of the following criteria is met:
   a. The requested medication will be used as a single agent
   b. The requested medication will be used in combination with lenalidomide in members who have high risk disease

B. Light Chain Amyloidosis

Authorization of 12 months may be granted for the treatment of light chain amyloidosis in either of the following settings:
1. For newly diagnosed members when used in combination with bortezomib, cyclophosphamide and dexamethasone or as a single agent.
2. For relapsed or refractory disease.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Multiple Myeloma

Authorization for 12 months may be granted for multiple myeloma when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member meets any of the following criteria:
   a. The requested drug will be used in combination with bortezomib, thalidomide, and dexamethasone and the member has not received a maximum of 16 doses
   b. The member is receiving benefit from therapy. Benefit is defined as:
      i. No evidence of unacceptable toxicity while on the current regimen or
      ii. No evidence of disease progression while on the current regimen

B. Light Chain Amyloidosis

Authorization for 12 months may be granted for light chain amyloidosis when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication
2. For members requesting reauthorization for newly diagnosed light chain amyloidosis, the maximum treatment duration is 24 months
3 The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen or
    b. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Darzalex Faspro.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
3. NCCN Guideline: Systemic light chain amyloidosis
4. NCCN Guideline: Multiple myeloma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Darzalex Faspro are covered in addition to the following:

A. Systemic light chain amyloidosis
B. In combination with other systemic therapies where IV daratumumab is recommended

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Darzalex Faspro as a single agent for newly diagnosed, relapsed, or refractory systemic light chain amyloidosis can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Darzalex Faspro as a single agent or in combination with other systemic therapies for the treatment of multiple myeloma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Darzalex Faspro [package insert]. Horsham, PA: Janssen Biotech Inc; November 2022.
2. The NCCN Drugs & Biologics Compendium® ©2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed December 14, 2023.

ELAHERE (mirvetuximab soravtansine-gynx)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Elahere is indicated for the treatment of adult patients with folate receptor-alpha positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Documentation of testing or laboratory results confirming folate receptor-alpha status, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Authorization of 12 months may be granted for treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer as a single agent or in combination with bevacizumab when all of the following criteria are met:
1. Member has folate receptor-alpha positive disease
2. Member has platinum-resistant disease
3. Member has received at least one prior systemic therapy

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen and
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Elahere.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)

d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guidelines: Ovarian cancer including fallopian tube cancer and primary peritoneal cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elahere are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Elahere to treat epithelial ovarian, fallopian tube, or primary peritoneal cancer with Elahere in combination with bevacizumab can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Elahere [package insert]. Waltham, MA: ImmunoGen, Inc.; November 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed September 08, 2023.

ELAPRASE (idursulfase)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Elaprase is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Elaprase has been shown to improve walking capacity in patients 5 years and older. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with Elaprase has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of Elaprase have not been established in pediatric patients less than 16 months of age.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: iduronate-2-sulfatase enzyme assay or genetic testing results supporting diagnosis.
B. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

III. CRITERIA FOR INITIAL APPROVAL

Mucopolysaccharidosis II (MPS II, Hunter syndrome)
Authorization of 12 months may be granted for treatment of MPS II (Hunter syndrome) when the diagnosis of MPS II was confirmed by enzyme assay demonstrating a deficiency of iduronate-2-sulfatase enzyme activity or by genetic testing.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Elaprase.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. Recognition and diagnosis of mucopolysaccharidosis II (Hunter Syndrome).
4. Multidisciplinary management of Hunter syndrome.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elaprase are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assays or genetic testing to confirm the diagnosis prior to using Elaprase to treat MPS II can be found in a guideline published by Martin et al. Diagnosis can be confirmed by assessing the enzyme activity on cultured fibroblasts, leukocytes, plasma, or serum. Absent or low I2S activity in males is diagnostic of Hunter syndrome. Mutation analysis may be used to confirm Hunter syndrome in males. Mutations that result in complete absence of the enzyme or its activity are commonly associated with Hunter syndrome with neurologic involvement.

VII. REFERENCES

1. Elaprase [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; September 2021.
2. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. Pediatrics. 2009;124(6):e1228-e1239.
3. Martin R, Beck M, Eng C, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). Pediatrics. 2008;121(2). Available at: www.pediatrics.org/cgi/content/full/121/2/e377.

ELELYSO (taliglucerase alfa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Elelyso is indicated for the treatment of patients 4 years and older with a confirmed diagnosis of Type 1 Gaucher disease.

B. Compendial Uses
1. Gaucher disease type 2
2. Gaucher disease type 3

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For initial requests: beta-glucocerebrosidase enzyme assay or genetic testing results supporting diagnosis.

III. CRITERIA FOR INITIAL APPROVAL

A. Gaucher disease type 1
Authorization of 12 months may be granted for treatment of Gaucher disease type 1 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

B. Gaucher disease type 2
Authorization of 12 months may be granted for treatment of Gaucher disease type 2 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

C. Gaucher disease type 3
Authorization of 12 months may be granted for treatment of Gaucher disease type 3 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as not experiencing an inadequate response or any intolerable adverse events from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Elelyso.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Gaucher disease: GeneReviews.
4. Revised recommendations for the management of Gaucher disease in children.
5. Management of neuronopathic Gaucher disease: revised recommendations. European Working Group on Gaucher Disease.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elelyso are covered in addition to the following:

A. Gaucher disease type 2
B. Gaucher disease type 3

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The diagnosis of Gaucher disease relies on demonstration of deficient glucocerebrosidase (glucosylceramidase) enzyme activity in peripheral blood leukocytes or other nucleated cells or by the identification of biallelic pathogenic variants in *GBA1* (formerly *GBA*). (Pastores and Hughes).

Support for using Elelyso to treat Gaucher disease type 2 can be found in the National Organization for Rare Disorders Guide to Rare Disorders. Enzyme replacement therapy (ERT) is effective for type 1 disease. Anemia and thrombocytopenia improve, hepatomegaly and splenomegaly are reduced, and skeletal damage is ameliorated with ERT. These systemic manifestations also improve with ERT in patients with type 2 and 3 disease. However, it should be noted that ERT does not reverse brain damage in patients with type 2 disease.

Support for using Elelyso to treat Gaucher disease type 3 can be found in the Revised Recommendations for the Management of Gaucher Disease by Kaplan et al. The guideline indicates symptomatic children with types 1 or 3 disease should receive enzyme replacement therapy, which will prevent debilitating and often irreversible disease progression and allow those with non-neuropathic disease to lead normal healthy lives. Additionally, the European Working Group on Gaucher Disease recommends ERT in patients with chronic neuronopathic Gaucher disease, siblings of patients with chronic neuronopathic Gaucher disease who are proven to have Gaucher disease, patients with certain high-risk genotypes, and patients who experienced the onset of severe systemic Gaucher disease at age 2 or younger.

VII. REFERENCES

1. Elelyso [package insert]. New York, NY: Pfizer, Inc; May 2023.
2. Zimran A, Brill-Almon E, Chertkoff R, et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease. *Blood*. 2011;118:5767-5773.
3. Pastores GM, Hughes DA. Gaucher Disease. 2000 July 27 [Updated March 9, 2023]. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2023.
4. Kaplan P, Baris H, De Meirleir L, et al. Revised recommendations for the management of Gaucher disease in children. *Eur J Pediatr.* 2013;172:447-458.
5. Vellodi A, Tylki-Szymanska A, Davies EH, et al. Management of neuronopathic Gaucher disease: revised recommendations. European Working Group on Gaucher Disease. *J Inherit Metab Dis*. 2009;32(5):660.

6. National Organization for Rare Disorders. (2003). NORD guide to rare disorders. Philadelphia: Lippincott Williams & Wilkins.

ELEVIDYS (delandistrogene moxeparvovec-rokl)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Elevidys is indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.

This indication is approved under accelerated approval based on expression of Elevidys micro-dystrophin in skeletal muscle observed in patients treated with Elevidys. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Genetic test results confirming the DMD diagnosis.
B. Medical records (e.g., chart notes, lab reports) documenting the member's ambulation status.

III. EXCLUSIONS

Coverage will not be provided for members with the following exclusion:
A. Deletion in exon 8 and/or exon 9 in the *DMD* gene.

IV. CRITERIA FOR INITIAL APPROVAL

Duchenne muscular dystrophy (DMD)
Authorization of 1 month for one dose total may be granted for treatment of Duchenne muscular dystrophy when all of the following criteria are met:
A. Member is 4 to 5 years of age (inclusive).
B. Member is ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent).
C. Member has a definitive diagnosis of DMD confirmed via genetic testing.
D. Member has anti-recombinant adeno-associated virus serotype rh74 (anti-AAVrh74) total binding antibody titers of < 1:400.
E. Member has not received treatment with Elevidys previously.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Elevidys.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex

c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elevidys are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Elevidys [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; June 2023.

ELFABRIO (pegunigalsidase alfa-iwxj)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Elfabrio is indicated for the treatment of adults with confirmed Fabry disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: alpha-galactosidase enzyme assay or genetic testing results supporting diagnosis. In the case of obligate carriers, the documentation must be submitted for the parent.
B. Continuation requests: lab results or chart notes documenting a benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

Fabry disease
Authorization of 12 months may be granted for treatment of Fabry disease when the diagnosis of Fabry disease was confirmed by enzyme assay demonstrating a deficiency of alpha-galactosidase enzyme activity or by genetic testing, or the member is a symptomatic obligate carrier.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., reduction in plasma globotriaosylceramide [Gb3] or Gb3 inclusions, improvement and/or stabilization in renal function, pain reduction).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Elfabrio.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document.
4. Fabry disease revisited: Management and treatment recommendations for adult patients.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elfabrio are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The diagnosis of Fabry disease can be confirmed using several methods. According to Biegstraaten et al, a definite diagnosis of Fabry disease is made when the patient has a GLA mutation, deficiency of alpha-galactosidase enzyme activity in leukocytes and one of the following: one or more characteristic sign(s) of Fabry disease (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma), an increase in plasma (lyso)Gb3, or a family member with a definite Fabry disease diagnosis carrying the same GLA mutation. Additionally, Ortiz et al report a larger group of patients have later-onset phenotypes and varying levels of residual alpha-galactosidase enzyme activity. Severe clinical manifestations have been reported in at least 43% of obligate carrier women. Enzyme replacement therapy should be considered in these cases if there is laboratory, histological, or imaging evidence of injury to the kidney, heart or central nervous system regardless of the alpha-galactosidase enzyme activity.

VII. REFERENCES

1. Elfabrio [package insert]. Cary, NC: Chiesi USA, Inc.; May 2023.
2. Biegstraaten M, Arngrimsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet J Rare Dis.* 2015; 1036.
3. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123(4):416-427.

ELIGARD (leuprolide acetate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Palliative treatment of advanced prostate cancer

B. Compendial Uses
1. Prostate cancer
2. Recurrent androgen receptor-positive salivary gland tumors
3. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Prostate cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

B. Gender dysphoria
1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member has reached Tanner stage 2 of puberty or greater.
2. Authorization of 12 months may be granted for gender transition when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member will receive the requested medication concomitantly with gender-affirming hormones.

C. Salivary gland tumors
Authorization of 12 months may be granted for treatment of recurrent salivary gland tumors when the tumor is androgen receptor positive.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat gender dysphoria.
C. The member is receiving benefit from therapy.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat prostate cancer.

C. The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced an unacceptable toxicity.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat salivary gland tumors.
C. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Eligard.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
3. NCCN Guideline: Prostate cancer
4. NCCN Guideline: Head and neck cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Eligard are covered in addition to the following:
1. Prostate cancer other than advanced prostate cancer
2. Salivary gland tumors
3. Gender dysphoria

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Eligard to treat prostate cancer and salivary gland tumors can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Eligard for gender dysphoria can be found in the Endocrine Society Clinical Practice guideline for Endocrine Treatment of gender-dysphoric/gender-incongruent persons. The guidelines support GnRH agonist use in both transgender males and transgender females. Specific products are not listed; therefore, coverage is applied to the entire class of GnRH agonists.
Support for using Eligard for gender dysphoria can also be found in the World Professional Association for Transgender Health (WPATH). According to the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, prescribing GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (defined as past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy. PATH also recommends to begin pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

WPATH recommends health care professionals prescribe progestins or a GnRH agonist for eligible transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.
WPATH also recommends health care professionals prescribe testosterone-lowering medications (including GnRH agonists) for eligible transgender and gender diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.

VI. REFERENCES

1. Eligard [package insert]. Fort Collins, CO: Tolmar Pharmaceuticals; April 2019.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed February 2, 2023.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Prostate Cancer. Version 3.2022. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 2, 2023.
4. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017:102(11):3869–3903.
5. Gender Identity Research and Education Society. Guidance for GPs and other clinicians on the treatment of gender variant people. UK Department of Health. Published March 10, 2008.
6. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, 8th version. ©2022 World Professional Association for Transgender Health. Available at http://www.wpath.org.
7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Head and Neck tumors. Version 1.2022. http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed February 2, 2023.

ELREXFIO (elranatamab-bcmm)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Elrexfio is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Multiple Myeloma
Authorization of 12 months may be granted for treatment of relapsed or refractory multiple myeloma in members who have received at least 4 prior therapies, including at least one drug from each of the following categories:
1. Anti-CD38 monoclonal antibody (e.g., daratumumab)
2. Proteasome inhibitor (e.g., bortezomib, ixazomib, carfilzomib)
3. Immunomodulatory agent (e.g., lenalidomide, pomalidomide)

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Elrexfio.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elrexfio are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Elrexfio [package insert]. New York, NY: Pfizer Inc.; August 2023.

ELZONRIS (tagraxofusp-erzs)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Elzonris is a CD123-directed cytotoxin indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.

B. Compendial Use
Blastic plasmacytoid dendritic cell neoplasm (BPDCN)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For initial requests: Medical record documentation that supports a confirmed diagnosis of BPDCN.

III. CRITERIA FOR INITIAL APPROVAL

Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Authorization of 12 months may be granted for treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) when used as a single agent.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen and
   ii. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Elzonris.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Acute myeloid leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elzonris are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Elzonris as a single agent to treat BPDCN can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Elzonris [package insert]. New York, NY: Stemline Therapeutics, Inc.; July 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed January 6, 2024.

EMPLICITI (elotuzumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one to three prior therapies.
   2. Empliciti is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

B. Compendial Uses
   Therapy for previously treated multiple myeloma for relapsed or progressive disease in combination with bortezomib and dexamethasone

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Multiple Myeloma
Authorization of 12 months may be granted for the treatment of previously treated multiple myeloma when any of the following criteria are met:
1. The requested medication will be used in combination with lenalidomide and dexamethasone
2. The requested medication will be used in combination with bortezomib and dexamethasone
3. The requested medication will be used in combination with pomalidomide and dexamethasone in members who have received at least two prior therapies, including an immunomodulatory agent and a proteasome inhibitor

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Empliciti
B. Empliciti is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
   1. No unacceptable toxicity while on the current regimen, AND
   2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Empliciti.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex

c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Multiple myeloma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Empliciti are covered in addition to using Empliciti in combination with bortezomib and dexamethasone.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Empliciti in combination with bortezomib and dexamethasone to treat multiple myeloma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Empliciti [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; March 2022.
2. The NCCN Drugs & Biologics Compendium 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed September 21, 2023.

ENHERTU (fam-trastuzumab deruxtecan-nxki)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. HER2-positive Breast Cancer
   Enhertu is indicated for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive [immunohistochemistry score (IHC) 3+ or in situ hybridization test (ISH) positive] breast cancer who have received a prior anti-HER2 based regimen either:
   i. in the metastatic setting, or
   ii. in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
2. HER2-low Breast Cancer
   Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-low [immunohistochemistry score (IHC) 1+ or IHC 2+/ in situ hybridization test (ISH) negative] breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
3. Gastric or Gastroesophageal Junction Adenocarcinoma
   Enhertu is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.
4. Non-Small Cell Lung Cancer (NSCLC)
   Enhertu is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
5. Solid Tumors
   Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

B. Compendial Uses
1. HER2-positive breast cancer, treatment of recurrent disease
2. HER2-low breast cancer, treatment of recurrent disease
3. Non-small cell lung cancer with HER2 mutations, treatment of recurrent and advanced disease
4. HER2-amplified colorectal cancer (including appendiceal and anal adenocarcinoma)
5. HER2-positive esophageal, gastric, or gastroesophageal junction cancer
6. HER2-positive cervical cancer
7. HER2-positive endometrial carcinoma
8. HER2-positive salivary gland tumor
9. HER2-positive ovarian cancer
10. HER2-positive vaginal cancer
11. HER2-positive biliary tract cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: human epidermal growth factor receptor 2 (HER2) status (e.g., immunohistochemistry (IHC) score, in situ hybridization (ISH) test).

III. CRITERIA FOR INITIAL APPROVAL

A. Breast Cancer

Authorization of 12 months may be granted for treatment of breast cancer when either of the following criteria are met:

1. Member has HER2-positive breast cancer and meets all of the following criteria:
    i. The disease had no response to preoperative systemic therapy, or the disease is recurrent, metastatic, or unresectable
    ii. The requested medication will be used as a single agent.
2. Member has HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer and meets all of the following criteria:
    i. The disease had no response to preoperative systemic therapy, or the disease is recurrent, metastatic or unresectable
    ii. The member has tried at least one prior chemotherapy
    iii. The requested medication will be used as a single agent

B. Non-Small Cell Lung Cancer

Authorization of 12 months may be granted for subsequent treatment of non-small cell lung cancer with HER2 (ERBB2) positive mutations when both of the following criteria are met:

1. The disease is recurrent, advanced, metastatic or unresectable
2. The requested medication will be used as a single agent

C. Colorectal Cancer

Authorization of 12 months may be granted for treatment of colorectal cancer (including appendiceal and anal adenocarcinoma) with HER2-amplified disease as a single agent when the requested medication will be used as subsequent therapy for progression of advanced or metastatic disease.

D. Esophageal, Gastric or Gastroesophageal Junction Adenocarcinoma

Authorization of 12 months may be granted for members with HER2-positive disease who are not surgical candidates or for subsequent treatment of HER2-positive locally advanced, recurrent or metastatic esophageal, gastric or gastroesophageal junction adenocarcinoma as a single agent.

E. Cervical Cancer

Authorization of 12 months may be granted for subsequent treatment of recurrent or metastatic HER2-positive (IHC 3+ or 2+) cervical cancer when used as a single agent.

F. Endometrial Carcinoma

Authorization of 12 months may be granted for subsequent treatment of recurrent HER2-positive (IHC 3+ or 2+) endometrial carcinoma when used as a single agent.

G. Salivary Gland Tumor

Authorization of 12 months may be granted for treatment of recurrent, unresectable, or metastatic HER2-positive salivary gland tumor when used as a single agent.

H. Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Authorization of 12 months may be granted for treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer when all of the following criteria are met:

1. The member has platinum-resistant persistent or recurrent disease
2. The disease is HER2-positive (IHC 3+ or 2+)
3. The requested medication will be used as a single agent

I. Solid Tumors

Authorization of 12 months may be granted for treatment of solid tumors when all of the following criteria are met:

1. The disease is unresectable or metastatic
2. The tumor is HER2-positive (IHC 3+)
3. The member received prior systemic treatment and has no satisfactory alternative treatment options

J. Vaginal Cancer
Authorization of 12 months may be granted for subsequent treatment of recurrent or metastatic HER2-positive (IHC 3+ or 2+) vaginal cancer when used as a single agent.

K. Biliary Tract Cancer
Authorization of 12 months may be granted for subsequent treatment of unresectable or resected gross residual (R2) disease or metastatic HER2-positive (IHC 3+) biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer) when used as a single agent.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section III when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Enhertu
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Breast Cancer
4. NCCN Guideline: Non-Small Cell Lung Cancer
5. NCCN Guideline: Colon Cancer
6. NCCN Guideline: Esophageal and Esophagogastric Junction Cancers
7. NCCN Guideline: Gastric Cancer
8. NCCN Guideline: Cervical Cancer
9. NCCN Guideline: Uterine Neoplasms
10. NCCN Guideline: Head and Neck Cancers
11. NCCN Guideline: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
12. NCCN Guideline: Vaginal Cancer
13. NCCN Guideline: Biliary Tract Cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Enhertu are covered in addition to treatment of recurrent disease for HER2-positive and HER2-low breast cancer, treatment of recurrent and advanced non-small cell lung cancer with HER2 mutations, HER2-amplified colorectal cancer, HER2-positive esophageal, gastric, or gastroesophageal junction cancer, HER2-positive cervical cancer, HER2-positive endometrial carcinoma, HER2-positive salivary gland tumor, HER2-positive ovarian cancer, HER2-positive vaginal cancer, and HER2-positive biliary tract cancer.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Enhertu to treat breast cancer, non-small cell lung cancer, colorectal cancer, esophageal, gastric, and gastroesophageal junction cancer, cervical cancer, endometrial carcinoma, salivary gland tumors, ovarian cancer, vaginal cancer, and biliary tract cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and

biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Enhertu [package insert]. Basking Ridge, NJ; Daiichi Sankyo, Inc; April 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc.. Available at http://www.nccn.org. Accessed April 25, 2024.

ENJAYMO (sutimlimab-jome)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Enjaymo is indicated for the treatment of hemolysis in adults with cold agglutinin disease (CAD).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests: chart notes, medical records or test results documenting:
   1. Lactate dehydrogenase (LDH) level above the upper limit of normal and haptoglobin level below the lower limit of normal
   2. Positive polyspecific direct antiglobulin test (DAT) result
   3. Monospecific DAT result strongly positive for C3d
   4. Cold agglutinin titer of 1:64 or higher measured at 4°C
   5. DAT result for IgG of 1+ or less
   6. Secondary CAD has been ruled out (e.g., cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy)
B. For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

III. CRITERIA FOR INITIAL APPROVAL

Cold Agglutinin Disease (CAD)
Authorization of 6 months may be granted for the treatment of cold agglutinin disease (CAD) when all of the following criteria are met:
A. Confirmed diagnosis of primary cold agglutinin disease (CAD) based on all of the following:
   1. Evidence of hemolysis as indicated by both of the following:
      i. Lactate dehydrogenase (LDH) level above the upper limit of normal
      ii. Haptoglobin level below the lower limit of normal
   2. Positive polyspecific direct antiglobulin test (DAT) result
   3. Monospecific DAT result strongly positive for C3d
   4. Cold agglutinin titer of 1:64 or higher measured at 4°C
   5. DAT result for IgG of 1+ or less
B. Secondary CAD has been ruled out (e.g., cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy)

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Enjaymo.

B. Enjaymo is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen, and
    2. No evidence of disease progression while on the current regimen, and
    3. Positive response to therapy (e.g., improvement in hemoglobin levels, improvement in markers of hemolysis [e.g., bilirubin, haptoglobin, lactate dehydrogenase [LDH], reticulocyte count], a reduction in blood transfusions).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Enjaymo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Enjaymo are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Enjaymo [package insert]. Waltham, MA: Bioverativ USA Inc.; March 2023.
2. Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, Kuter DJ, Jilma B, Tvedt THA, Fruebis J, et al. Sutimlimab in cold agglutinin disease. N Engl J Med. 2021;384(14):1323–34.
3. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020;41:100648.

ENTYVIO (vedolizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Adult patients with moderately to severely active ulcerative colitis (UC)
   2. Adult patients with moderately to severely active Crohn's disease (CD)

B. Compendial Uses
   Immune checkpoint inhibitor-related toxicity

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Ulcerative colitis (UC) and Crohn's disease (CD)
   For continuation requests: Chart notes or medical record documentation supporting positive clinical response to therapy or remission.

B. Immune checkpoint inhibitor-related toxicity (initial requests only)
   Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Ulcerative colitis (UC)
Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

B. Crohn's disease (CD)
Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

C. Immune checkpoint inhibitor-related toxicity
Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when the member meets either of the following criteria:
1. Member has not responded to systemic corticosteroids or infliximab.
2. Member has moderate or severe diarrhea or colitis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Ulcerative colitis (UC)

Authorization for 12 months may be granted for moderately to severely active ulcerative colitis when both of the following criteria are met:

1. The member is currently receiving therapy with Entyvio.
2. The member is receiving benefit from therapy. Benefit is defined as one of the following:
    i. Member has achieved or maintained remission.
    ii. Member has achieved or maintained a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:
        a. Stool frequency
        b. Rectal bleeding
        c. Urgency of defecation
        d. C-reactive protein (CRP)
        e. Fecal calprotectin (FC)
        f. Appearance of the mucosa on endoscopy, computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound
        g. Improvement on a disease activity scoring tool (e.g., Ulcerative Colitis Endoscopic Index of Severity [UCEIS], Mayo score)

B. Crohn's disease (CD)

Authorization for 12 months may be granted for moderately to severely active Crohn's disease when both of the following criteria are met:

1. The member is currently receiving therapy with Entyvio.
2. The member is receiving benefit from therapy. Benefit is defined as one of the following:
    i. Member has achieved or maintained remission.
    ii. Member has achieved or maintained a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:
        a. Abdominal pain or tenderness
        b. Diarrhea
        c. Body weight
        d. Abdominal mass
        e. Hematocrit
        f. Appearance of the mucosa on endoscopy, computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound
        g. Improvement on a disease activity scoring tool (e.g., Crohn's Disease Activity Index [CDAI] score)

C. Immune checkpoint inhibitor-related toxicity

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Entyvio.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Management of Immunotherapy-Related Toxicities
4. An evidence-based systematic review on medical therapies for inflammatory bowel disease.
5. American College of Gastroenterology (ACG) Clinical Guideline: Management of Crohn's Disease in Adults
6. American Gastroenterological Association (AGA) Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis

7. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Entyvio are covered in addition to immune checkpoint inhibitor-related toxicity.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the continuation of therapy criteria for Crohn's disease can be found in the American College of Gastroenterology guidelines for the management of Crohn's disease (CD) and a review article by Talley et al. The American College of Gastroenterology lists mucosal healing as determined by endoscopy as a goal of therapy. Mucosal healing is defined as an absence of ulceration and endoscopic scoring systems have been developed to quantify degree of ulceration and inflammation in patients with CD within the reach of the colonoscope. There are a limited number of studies that have examined the long-term impact of mucosal healing on the clinical course of disease. In patients with early-stage CD, complete mucosal healing after 2 years of therapy predicts sustained steroid-free, clinical remission 3 and 4 years out from initiation of treatment. Other clinical outcomes associated with mucosal healing in CD have been decreased surgery and hospitalizations. The simple endoscopic score for Crohn's disease (SES-CD) scoring system has been used prospectively to assess mucosal healing in patients treated with anti-tumor necrosis factor (anti-TNF) therapy as well as with anti-TNF/thiopurines combination therapy, demonstrating that changes can be measured; furthermore, there is a strong correlation between improvement in the SES-CD (mucosal) healing and clinical remission. Better clinical outcomes such as decreased hospitalizations, surgery, and steroid use is associated with improved findings on CTE and MRE in patients with small bowel Crohn's disease.
Improvement in the symptoms of CD is also a goal of therapy. The most common symptom of Crohn's disease is chronic diarrhea, but some patients may not experience this symptom. Abdominal pain, often localized to the right lower quadrant of the abdomen and worsened postprandially, is common. Improvement in these symptoms as well as fatigue, weight loss, anemia, and recurrent fistulas is considered sufficient evidence to continue with therapy.

Support for the continuation of therapy for ulcerative colitis can be found in the American Gastroenterological Association guidelines for the management of moderate to severe ulcerative colitis. The Truelove and Witts criteria for classifying the severity of UC include the number of stools per day, the presence of blood in the stool, hemoglobin, colonic features on radiograph and other clinical signs such as abdominal tenderness and distention. Improvement in any of these factors while on Entyvio therapy is sufficient to continue using the requested medication.
Additionally, the American College of Gastroenterology indicates an elevation in C-reactive protein and erythrocyte sedimentation rate are indicators of active UC. The guidelines go on to indicate the goal of treatment is to achieve mucosal healing (defined as resolution of inflammatory changes (Mayo endoscopic subscore 0 or 1) to increase the likelihood of sustained steroid-free remission and prevent hospitalizations and surgery). Fecal calprotectin can be used as a surrogate for endoscopy when endoscopy is not feasible or available to assess for mucosal healing. If the patient's condition appears to be improving based on either of these factors, it is then considered acceptable to continue using the requested medication.

Support for using Entyvio for immune checkpoint inhibitor-related toxicities can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline supports the use of Entyvio for the management of mild (G1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin. Entyvio can also be used for the management of immunotherapy-related moderate (G2) and severe (G3-4) diarrhea or colitis.

VII. REFERENCES

1. Entyvio [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; June 2022.
2. Talley NJ, Abreu MT, Achkar J, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(Suppl 1):S2-S25.
3. Lichtenstein GR, Loftus Jr EV, Isaacs KI, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018;113:481-517.

4. Rubin DT, Ananthakrishnan AN, et al. 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol.* 2019;114:384-413.
5. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 16, 2023.
6. NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 1.2022. Available at: www.nccn.org. Accessed January 16, 2023.
7. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Guideline Update. *J Clin Oncol.* 2021; 39(36):4073-4126.
8. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology*. 2020; 158:1450-1461.
9. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. *Gastroenterology*. 2021; 160: 2496-2508.

EPKINLY (epcoritamab- bysp)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Epkinly is indicated for the treatment of adult patients with relapsed or refractory diffuse large b-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B–cell lymphoma (HGBL), after two or more lines of systemic therapy.

B. Compendial Uses
B-Cell Lymphomas:
1. Diffuse Large B-Cell Lymphomas
2. High Grade B-Cell Lymphomas
3. Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma
4. Human Immunodeficiency Virus (HIV)- Related B-Cell Lymphomas
   a. HIV-related diffuse large B-cell lymphoma
   b. Primary effusion lymphoma
   c. Human Herpes Virus Type 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specified
5. Monomorphic Post-Transplant Lymphoproliferative Disorders

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

B-Cell Lymphomas
Authorization of 12 months may be granted for treatment of B-cell lymphoma after at least 2 prior lines of systemic therapy when the member has partial response, no response, progressive, relapsed or refractory disease with any of the following subtypes:
A. Diffuse Large B-Cell Lymphoma (DLBCL)
B. High Grade B- Cell Lymphoma
C. Histologic Transformation of Indolent Lymphoma to DLBCL
D. HIV-Related B- Cell Lymphoma including HIV-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL, not otherwise specified when the requested medication is used as a single agent
E. Monomorphic Post-Transplant Lymphoproliferative Disorder when the requested medication is used as a single agent

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II

3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Epkinly.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Epkinly are covered in addition to the following:

1. Diffuse Large B-Cell Lymphomas
2. High-grade B-Cell Lymphomas
3. Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma
4. Human Immunodeficiency Virus (HIV)- Related B-Cell Lymphomas
    a. HIV-related diffuse large B-cell lymphoma
    b. Primary effusion lymphoma
    c. Human Herpes Virus Type 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specified
5. Monomorphic Post-Transplant Lymphoproliferative Disorders

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Epkinly to treat HIV-related B-cell lymphomas, and monomorphic post-transplant lymphoproliferative disorders can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Epkinly to treat partial response, no response, or progressive diffuse large B-cell lymphoma, high-grade B-cell lymphoma, and histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma in addition to the FDA-approved indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Epkinly [package insert]. Plainsboro, NJ: Genmab US, Inc.; May 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed June 5, 2023.

EPOGEN, PROCRIT, RETACRIT (epoetin alfa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Epoetin alfa is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.
2. Epoetin alfa is indicated for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL.
3. Epoetin alfa is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
4. Epoetin alfa is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Epoetin alfa is not indicated for patients who are willing to donate autologous blood preoperatively.

Limitations of Use:
1. Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being.
2. Epoetin alfa is not indicated for use:
   - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
   - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
   - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
   - In patients scheduled for surgery who are willing to donate autologous blood.
   - In patients undergoing cardiac or vascular surgery.
   - As a substitute for RBC transfusions in patients who require immediate correction of anemia.

Note: Use in members on dialysis is covered under the Medicare Part B dialysis benefit and is excluded from coverage under this policy.

B. Compendial Uses
1. Anemia in members with myelodysplastic syndromes (MDS)
2. Anemia in epidermolysis bullosa
3. Anemia in rheumatoid arthritis
4. Anemia due to hepatitis C treatment with ribavirin in combination with either interferon alfa or peginterferon alfa
5. Anemia in porphyria cutanea tarda
6. Anemia in members whose religious beliefs forbid blood transfusions
7. Beta thalassemia
8. Prophylaxis of anemia of prematurity
9. Iron overload
10. Symptomatic anemia in members with primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis
11. Anemia due to radiation
12. Anemia due to puerperium
13. Anemia due to multiple myeloma
14. Cancer patients who are undergoing palliative treatment
15. Blood unit collection for autotransfusion

C. Nationally Covered Indication
Centers for Medicare and Medicaid Services guidelines provide coverage for epoetin alfa for anemia secondary to myelosuppressive chemotherapy based on the criteria in Sections II, III, and IV.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

The following exclusions criteria apply to members requesting use for anemia due to concomitant myelosuppressive chemotherapy:

A. The anemia is due to folate, B-12, or iron deficiency.
B. The anemia is due to hemolysis, bleeding, or bone marrow fibrosis.
C. The anemia is due to treatment for acute myelogenous leukemia, chronic myelogenous leukemia, or erythroid cancers.
D. The anemia is due to cancer not related to cancer treatment.
E. The anemia is due to treatment with radiotherapy only.
F. Prophylactic use to prevent chemotherapy-induced anemia.
G. Prophylactic use to reduce tumor hypoxia.
H. Use in members with erythropoietin-type resistance due to neutralizing antibodies.
I. Members with uncontrolled hypertension.

III. CRITERIA FOR INITIAL APPROVAL

Note: Requirements regarding hemoglobin level exclude values due to a recent transfusion.

A. Anemia due to chronic kidney disease
Authorization of 12 weeks may be granted for the treatment of anemia due to chronic kidney disease in members not receiving dialysis with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

B. Anemia due to concomitant myelosuppressive chemotherapy
Authorization of 8 weeks may be granted for the treatment of anemia due to concomitant chemotherapy in members when all of the following criteria are met:

1. The member is receiving chemotherapy for a solid tumor, multiple myeloma, lymphoma, or lymphocytic leukemia.
2. The hemoglobin level immediately prior to initiation or maintenance of therapy is less than 10 g/dL or the hematocrit is less than 30%.
3. The starting dose is not greater than 450 U/kg per week or 40,000 units weekly.

C. Reduction of allogeneic red blood cell transfusion in members undergoing elective, noncardiac, nonvascular surgery
Authorization of 12 weeks may be granted for members scheduled to have an elective, noncardiac, nonvascular surgery when the pretreatment hemoglobin is > 10 to ≤ 13 g/dL.

D. Anemia due to zidovudine in HIV-infected members
Authorization of 12 weeks may be granted for the treatment of anemia in HIV-infected members currently receiving zidovudine with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

E. Anemia due to myelodysplastic syndrome
Authorization of 12 weeks may be granted for the treatment of anemia due to myelodysplastic syndrome in members with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

F. Anemia in epidermolysis bullosa
Authorization of 12 weeks may be granted for the treatment of anemia in members with epidermolysis bullosa whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

G. Anemia in rheumatoid arthritis
Authorization of 12 weeks may be granted for the treatment of anemia in rheumatoid arthritis in members whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

H. Anemia due to hepatitis C treatment
Authorization of 12 weeks may be granted for the treatment of anemia due to hepatitis C treatment in members who meet all of the following criteria:
1. The member's hemoglobin is less than 10 g/dL or hematocrit is less than 30%.
2. The member is receiving ribavirin in combination with either interferon alfa or peginterferon alfa.

I. Anemia in porphyria cutanea tarda
Authorization of 12 weeks may be granted for the treatment of anemia in members with porphyria cutanea tarda.

J. Anemia in members whose religious beliefs forbid blood transfusions
Authorization of 12 weeks may be granted for treatment of anemia in members whose religious beliefs forbid blood transfusions whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

K. Beta thalassemia
Authorization of 12 weeks may be granted for the treatment of anemia in members with beta thalassemia.

L. Prophylaxis of anemia of prematurity
Authorization of 12 weeks may be granted for the prophylaxis of anemia of prematurity in members less than 1 year of age.

M. Iron overload
Authorization of 12 weeks may be granted for the treatment of iron overload in combination with phlebotomy.

N. Anemia in myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis
Authorization of 12 weeks may be granted for the treatment of anemia due to myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis when all of the following criteria are met:
1. The member has a hemoglobin level less than 10 g/dL or a hematocrit less than 30%.
2. The member has an erythropoietin (EPO) level less than 500 mU/mL.

O. Anemia due to radiation
Authorization of 12 weeks may be granted for the treatment of anemia due to radiation.

P. Anemia during the puerperium
Authorization of 12 weeks may be granted for the treatment of anemia following childbirth.

Q. Anemia due to multiple myeloma
Authorization of 12 weeks may be granted for the treatment of anemia due to multiple myeloma.

S. Anemia due to cancer
Authorization of 12 weeks may be granted for the treatment of anemia in members who have cancer and are undergoing palliative treatment.

T. Blood unit collection for autotransfusion
Authorization of 12 weeks may be granted to increase the capacity for donation for future autologous transfusion prior to elective surgery.

IV. CONTINUATION OF THERAPY

Note: Requirements regarding current hemoglobin level exclude values due to a recent transfusion.

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization of 12 weeks may be granted for the treatment of anemia due to concomitant myelosuppressive chemotherapy when all of the following criteria are met:
   1. The member is currently receiving therapy with epoetin alfa.
   2. The member does not have any exclusions listed in Section II.
   3. The member has experienced at least a 1 g/dL increase in their hemoglobin or a 3% increase in their hematocrit.
   4. The member's hemoglobin is less than 11 g/dL or the prescriber will hold or reduce the dose of epoetin alfa to maintain a hemoglobin level sufficient to avoid transfusion.
   5. Treatment will not extend beyond 8 weeks following the final dose of myelosuppressive chemotherapy given in the member's current chemotherapy regimen.

B. Authorization of 12 weeks may be granted for all other indications when all of the following criteria are met:
   1. The member is currently receiving therapy with epoetin alfa.
   2. The member is receiving epoetin alfa for an indication listed in Section III.
   3. Epoetin alfa has been effective for treating the diagnosis or condition.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Epogen, Procrit and Retacrit.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease
4. Management of Cancer-Associated Anemia with Erythropoiesis-Stimulating Agents: American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) Clinical Practice Guideline Update
5. NCCN Guideline: Myelodysplastic syndromes
6. NCCN Guideline: Myeloproliferative neoplasms
7. NCCN Guideline: Hematopoietic growth factors
8. Medicare National Coverage Determinations (NCD) Manual

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Epogen, Procrit and Retacrit are covered in addition to the following:

A. Anemia in members with myelodysplastic syndromes (MDS)
B. Anemia in epidermolysis bullosa
C. Anemia in rheumatoid arthritis
D. Anemia due to hepatitis C treatment with ribavirin in combination with either interferon alfa or peginterferon alfa
E. Anemia in porphyria cutanea tarda
F. Anemia in members whose religious beliefs forbid blood transfusions
G. Beta thalassemia
H. Prophylaxis of anemia of prematurity
I. Iron overload
J. Symptomatic anemia in members with primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis
K. Anemia due to radiation
L. Anemia due to puerperium
M. Anemia due to multiple myeloma
N. Cancer patients who are undergoing palliative treatment
O. Blood unit collection for autotransfusion

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications (anemia due to chronic kidney disease, anemia due to zidovudine, anemia due to chemotherapy in members with cancer, reduction of allogenic RBC transfusions in members undergoing elective, noncardiac, nonvascular surgery) can be found in the manufacturer's prescribing information.

Support for using epoetin alfa to treat anemia due to myelodysplastic syndrome can be found in the National Comprehensive Cancer Network's (NCCN) guideline for myelodysplastic syndromes. The NCCN Guideline for myelodysplastic syndrome supports the use of epoetin alfa for the treatment of symptomatic anemia associated with lower risk (IPSS low/intermediate-1) disease with del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7). Epoetin alfa can also be used for the treatment of symptomatic anemia associated with lower risk (IPSS-R very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an *SF3B1* mutation), with serum erythropoietin (EPO) ≤ 500 mU/mL as either a single agent, or in combination with either lenalidomide or granulocyte-colony stimulating factor (G-CSF) following no response or erythroid response followed by loss of response to an erythropoiesis-stimulating agent (ESA) alone. Finally, epoetin alfa can be used as treatment of symptomatic anemia associated with lower risk (IPSS-R very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring sideroblasts ≥ 15% (or ring sideroblasts ≥5% with an *SF3B1* mutation), with serum EPO ≤ 500 mU/mL as a single agent or in combination with a G-CSF.

Support for using epoetin alfa to treat anemia associated with epidermolysis bullosa with concurrent intravenous iron can be found in a case report. Fridge and Vichinsky (1998) reported 4 of 5 children with epidermolysis bullosa and severe refractory anemia became transfusion-independent after treatment with erythropoietin and intravenous iron. Iron 10 to 20 milligrams (mg)/kilogram (kg) as iron dextran was administered monthly and erythropoietin was given in escalating doses of 150 to 350 units/kg 3 times per week. Another patient whose pretreatment erythropoietin level was high was treated with intravenous iron alone. All patients responded. Mean hemoglobin rose from 6.8 to 10.0 grams/deciliter (p=0.01) and hematocrit from 23.8% to 33.1% (p=0.03). One patient died of sepsis; the other 4 continue to receive treatment and have reported an improved quality of life, accelerated wound healing, and improvement in weight-for-height percentile.

Support for using epoetin alfa to treat anemia in patients with rheumatoid arthritis can be found in a Cochrane review. In the Cochrane review, Marti-Carvajal et al. (2013) evaluated the clinical benefits and harms of ESAs for anemia in rheumatoid arthritis. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (issue 7 2012), Ovid MEDLINE and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1948 to August 7, 2012), OVID EMBASE (1980 to August 7, 2012), LILACS (1982 to August 7, 2012), the Clinical Trials Search Portal of the World Health Organization, reference lists of the retrieved publications and review articles. They did not apply any language restrictions. These researchers included randomized controlled trials (RCTs) in patients aged 16 years or over, with a diagnosis of rheumatoid arthritis affected by anemia. They considered health-related quality of life, fatigue, and safety as the primary outcomes. Two authors independently performed trial selection, risk of bias assessment, and data extraction. They estimated difference in means with 95% confidence intervals (CIs) for continuous outcomes. They estimated risk ratios with 95% CIs for binary outcomes. These investigators included 3 RCTs with a total of 133 participants. All trials compared human recombinant erythropoietin (EPO), for different durations (8, 12 and 52 weeks), versus placebo. All RCTs assessed health-related quality of life. All trials had high or unclear risk of bias for most domains and were sponsored by the pharmaceutical industry. Two trials administered EPO by a subcutaneous route while the other used an intravenous route. These researchers decided not to pool results from trials, due to inconsistencies in the reporting of results. Health-related quality of life: subcutaneous EPO - 1 trial with 70 patients at 52 weeks showed a statistically significant difference in improvement of patient global assessment (median and interquartile range 3.5 (1.0 to 6.0) compared with placebo 4.5 (2.0 to 7.5) (p = 0.027) on a visual analog scale (VAS) scale (0 to 10)). The other shorter-term trials (12 weeks with subcutaneous EPO and 8 weeks with intravenous administration) did not find statistically significant differences between treatment and control groups in health-related quality of life outcomes. Change in hemoglobin (Hb): both trials of subcutaneous EPO showed a statistically significant difference in increasing Hb levels; at 52 weeks (1 trial, 70 patients), intervention Hb level (median of 134, interquartile range 110 to 158 g/L) compared with the placebo group level (median of 112, interquartile range 86 to 128 g/L) (p = 0.0001); at 12 weeks (1 trial, 24 patients) compared with placebo (difference in means of 8.00, 95 % CI: 7.43

to 8.57). at 52 weeks (1 trial, 70 patients), intervention Hb level (median of 134, interquartile range 110 to 158 g/L) compared with the placebo group level (median of 112, interquartile range; 86 to 128 g/L) (p = 0.0001); at 12 weeks (1 trial, 24 patients) compared with placebo (difference in means of 8.00, 95 % CI: 7.43 to 8.57). Intravenous EPO at 8 weeks showed no statistically significant difference in increasing hematocrit level for EPO versus placebo (difference in means of 4.69, 95 % CI: -0.17 to 9.55; p = 0.06). Information on withdrawals due to adverse events was not reported in 2 trials, and 1 trial found no serious adverse events leading to withdrawals. None of the trials reported withdrawals due to high blood pressure, or to lack of efficacy or to fatigue. The authors concluded that there is conflicting data for ESAs to increase quality of life and Hb level by treating anemia in patients with rheumatoid arthritis. However, this conclusion is based on RCTs with a high-risk of bias, and relies on trials assessing EPO. They stated that the safety profile of EPO is unclear; and future trials assessing ESAs for anemia in rheumatoid arthritis should be conducted by independent researchers and reported according to the consolidated standards of reporting trials (CONSORT) statements.

Support for using epoetin alfa to treat anemia due to combination therapy of ribavirin and interferon alfa or ribavirin and peginterferon alfa can be found in a prospective, double-blind, placebo-controlled trial of 185 patients by Afdhal et al. (2004). Patients (n=185) with hemoglobin (Hb) of 12 grams/deciliter (g/dL) or less who were receiving any combination of ribavirin and interferon alfa for chronic hepatitis C virus (HCV) infection were randomized to receive epoetin alfa (Procrit(R)) 40,000 units subcutaneously once weekly (n=93) or placebo (n=92) for 8 weeks. If a patient's Hb level had not increased by at least 1 g/dL after 4 weeks of treatment, the dose was increased to 60,000 units once weekly. At the end of the 8-week double-blind period, patients were eligible for enrollment to an open-label modified crossover phase if they were receiving epoetin alfa in the double-blind phase and had a Hb increase of at least 1 g/dL, or if they were receiving placebo in the double-blind phase and ended that phase with Hb of 12 g/dL or less or had a ribavirin dose reduction due to anemia. The primary endpoint was ribavirin dose maintenance at the end of the 8-week double-blind phase. Patients had been on HCV treatment for an average of 12 and 14 weeks in the epoetin alfa and placebo groups, respectively, at the time of randomization. Ribavirin dose was maintained in 88% of patients who received epoetin alfa compared to 60% of patients who received placebo (p less than 0.001). In addition, the ribavirin dose stayed the same or increased since the start of HCV therapy in 77% of patients on epoetin alfa and 46% of patients on placebo (p less than 0.001). Patients who received epoetin alfa in the double-blind phase and continued receiving it in the open-label phase maintained their mean ribavirin dose throughout the open-label phase. Patients who received placebo in the double-blind phase had a significant increase in their mean ribavirin dose after receiving epoetin alfa in the open-label phase (p less than 0.001). Hemoglobin significantly improved in the epoetin alfa group (10.8 +/0.8 g/dL to 13 +/1.3 g/dL) compared to the placebo group (10.8 +/- 1 g/dL to 10.9 +/- 1.1 g/dL) in the double-blind phase (p less than 0.001). Quality of life significantly improved in patients who received epoetin alfa compared to those who received placebo in the double-blind phase, as assessed with a linear analog scale assessment (LASA) and the Medical Outcomes Short Survey Form-36 (version 2). One case of cerebral thrombosis occurred that was possibly related to epoetin alfa. No differences in liver function or HCV viral loads were detected.

Support for using epoetin alfa to treat anemia in porphyria cutanea tarda can be found in a case report. Anderson et al. (1990) reported a woman with life threatening porphyria cutanea tarda associated hemodialysis achieved remission of the porphyria after initiation of erythropoietin therapy 150 units/kilogram. Plasma porphyrin levels decreased from 211 mcg/dl (normal less than 2 mcg/dl) to less than 10% of this level after four months of erythropoietin therapy and intermittent phlebotomy.

Support for using epoetin alfa to treat anemia in patients whose religious beliefs forbid blood transfusion is supported by several small studies. Atabek and colleagues (1995) studied twenty Jehovah’s Witness patients with post-surgical hematocrits below 25% treated with erythropoietin (plus standard iron and nutritional support), compared to 20 retrospective control patients maintained with iron and nutritional support alone. The patients receiving erythropoietin demonstrated a more rapid rise in hematocrit, particularly within the first week, which was sustained after two weeks. Thirteen patients received erythropoietin as 300 units/kg intravenously (IV) 3 times weekly for the first week, then 150 units/kg 3 times weekly during the second week; seven patients received 100 units/kg IV 3 times weekly for 2 weeks. Among all erythropoietin-treated patients, the mean hematocrit rose from 15.8% to 19.3% after one week, and to 22.5% after two weeks. Control patients demonstrated an initial fall from 12.8% to 12.5% at the end of one week, rising to 17.8% after two weeks. Results reached statistical significance only at the end of the first week.
Four Jehovah's Witness patients who either exhibited preoperative anemia or developed postoperative anemia refractory to endogenous erythropoietin were discharged from the hospital in good condition after treatment with recombinant human erythropoietin (EPO) 50 to 280 units per kilogram body weight daily. The fifth patient,

who exhibited no signs of systemic inflammation following emergency hemicolectomy, was also treated with intravenous iron, but not with erythropoietin. No predictor of response was identified in this series; therefore, use of erythropoietin in this patient subgroup would be based strictly on humanitarian grounds (Wolff et al., 1997).

Support for using epoetin alfa to treat transfusion-dependent beta-thalassemia is supported by a small study by Chaidos et al. (2004). Epoetin alpha improved transfusion requirements but not hemoglobin in patients with thalassemia in a small, open-label clinical trial. Patients (n=10; median age, 28.3 years; range, 18-45 years) of Hellenic origin with thalassemia major (n=5) or thalassemia intermedia (n=5) all required red blood cell (RBC) transfusions either regularly every 2 to 3 weeks (n=7) or sporadically (n=3) at baseline. All patients were on iron chelation therapy. Epoetin alpha (Eprex(R)) 150 international units/kilogram was administered subcutaneously 3 times per week for at least 12 weeks. Median transfusion requirements were significantly reduced from 30.54 (range, 11.92-41.03) to 24.56 (range, 1.52-32.39) milliliters of packed RBC per kilogram of body weight every 8 weeks (p=0.028) in the transfusion-dependent patients (n=7). Two patients with thalassemia major were discontinued from treatment after 12 weeks due to inadequate response. Hemoglobin values did not significantly change during treatment. In the 3 patients who were not transfusion-dependent at baseline, hemoglobin values increased from 7.1, 9.9, and 8.1 grams/deciliter (g/dL) to 8.5, 11, and 9.5 g/dL, respectively, after treatment.

Support for using epoetin alfa as prophylaxis against anemia associated with prematurity is supported by a randomized, placebo-controlled trial by Donato and colleagues (2000). One hundred and fourteen low-birth-weight infants (less than 1250 g) who received erythropoietin within 72 hours of birth saw improved hematocrit and reticulocyte counts compared to later initiation (2 weeks after birth), but it failed to affect overall transfusion requirements. Intravenous (IV) erythropoietin dosing was 1250 units/kg/week as 5 divided doses, along with oral iron and folic acid supplementation. The percentage of patients requiring transfusions, the number of transfusions per patient, and total phlebotomy losses did not differ statistically between the 2 study groups. A post hoc subgroup analysis determined that total per-patient transfusion requirements were significantly lower with early versus late erythropoietin initiation (3.4 vs 5.4) in infants with birth weight under 800 g and phlebotomy losses greater than 30 mL/kg.

Support for using epoetin alfa to treat iron overload in combination with phlebotomy is found in a small study by McCarthy et al. (1989). Five transfusion dependent hemodialysis patients suffering from iron overload were treated with erythropoietin (150 units/kilogram) and phlebotomy in an attempt to reduce iron stores and maintain a hematocrit of 25%. During the 18-week study period, total iron removal ranged from 732 to 2797 milligrams and mean serum ferritin decreased from 3189 +/- 1076 micrograms/liter (mcg/L) to 1676 +/- 342 mcg/L.

Support for using epoetin alfa to treat myelofibrosis-associated anemia can be found in the National Comprehensive Cancer Network's guideline for myeloproliferative neoplasms. The NCCN Guideline supports the use of epoetin alfa for the management of myelofibrosis-associated anemia with serum erythropoietin (EPO) less than 500 mU/mL.
In a small, open-label study by Cervantes and colleagues (2004), treatment with human recombinant erythropoietin (EPO) improved anemia in some patients with myelofibrosis. Patients (n=20; median age, 64.5 years (yr); range, 45-91 yr; median baseline hemoglobin (Hb) level, 8.9 grams/deciliter (g/dL); range, 7.7-10 g/dL; median baseline erythropoietin level, 81 units/liter (L); range, 8-282 units/L; baseline erythropoietin level less than 125 units/L, n=16) having myelofibrosis with myeloid metaplasia and anemia who were red blood cell (RBC) transfusion dependent (n=13) or had a Hb level of 10 g/dL or less initially received subcutaneous erythropoietin 10,000 units 3 days per week. Erythropoietin was increased to 20,000 units 3 days per week if a response was not obtained after 2 months and erythropoietin was discontinued in patients who did not experience a response at 3 months. Patients received RBC transfusions for overtly symptomatic anemia or Hb levels less than 8 g/dL; additionally, patients with inadequate iron status received oral iron supplements (100 milligrams/day). Most patients in this study (n=17) had received one or more prior therapies (hydroxyurea, n=11; danazol, n=10; anagrelide, n=4; splenectomy, n=3; interferon alfa, n=1; prednisone, n=1; reduced-intensity conditioning allogeneic stem-cell transplantation, n=1) which were discontinued prior to study enrollment due to lack of or inadequate response. Nine patients (45%) had a good response to erythropoietin therapy, with 4 patients (20%) experiencing a complete response (defined as no RBC transfusion requirements with normalization of Hb) and 5 patients (25%) experiencing a partial response (defined as a 50% or greater reduction in monthly RBC transfusions and a Hb level of greater than 10 g/dL for at least 8 weeks). Additionally, at a median follow-up of 12.5 months (range, 4-21 months), 4 patients (20%) continued to have a response. Lack of a RBC transfusion requirement and a higher baseline Hb level correlated with a

favorable response in a univariate analysis. Overall, erythropoietin therapy was well tolerated; although, increased splenomegaly was reported in 2 patients.

Support for using epoetin alfa to treat anemia due to radiation therapy is supported by a study by Sweeney et al. (1998). In a randomized, open-label Phase II study of 48 patients with carcinoma of the lung, uterine cervix, prostate or breast with associated anemia, epoetin alfa 200 units/kilogram/day for 5 consecutive days per week for up to 7 weeks during radiotherapy significantly increased hemoglobin levels as compared to a control group. The average pre- and post-radiotherapy hemoglobin values were 12.1 and 13.6 grams/deciliter (g/dL) in the erythropoietin group as compared to 10.7 and 11 g/dL in the control group (p = 0.001). This translates to a weekly mean increase of 0.4 g/dL with epoetin alfa. Overall, 42% and 0% of the active and control groups, respectively, achieved the target hemoglobin level (15 g/dL in men, 14 g/dL in women). Epoetin alfa somewhat attenuated the radiotherapy-induced decline in platelet counts. No between-group differences occurred with respect to quality-of-life scores or adverse effects. Further study is needed to determine the effect of epoetin alfa on clinically significant endpoints.

Support for using epoetin alfa to treat anemia during the puerperium is supported by a randomized, placebo-controlled trial (n=60) conducted by Breymann and colleagues (2000). The combination of intravenous (IV) erythropoietin (EPO) 300 units/kilogram/day plus IV iron sucrose 200 milligrams (mg)/day on days 1 to 4 postpartum was more effective than IV iron alone or oral elemental iron sulfate 80 mg plus folic acid 0.35 mg twice daily in the treatment of postpartum anemia (hemoglobin less than 10 grams/deciliter). Subjects had lost an average of 806 milliliters of blood during delivery. On day 7, the reticulocyte count and increase in hemoglobin and hematocrit were significantly higher in the erythropoietin-iron group than either comparator group. As of day 14, erythropoietin recipients experienced an average 11.3% rise in hematocrit from baseline, significantly greater than iron alone. Transfusions were avoided in all three groups. No serious adverse effects occurred in any participant.

Support for using epoetin alfa to manage anemia associated with multiple myeloma can be found in the Management of cancer-associated anemia with erythropoiesis-stimulating agents: American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) clinical practice guideline update. In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA. Exercise caution in the use of ESAs concomitant with treatment strategies and diseases where risk of thromboembolic complications is increased. In all cases, blood transfusion is a treatment option that should be considered.
Additionally, a meta-analysis of 39 articles reported the effectiveness of erythropoietin in the treatment of anemia of end-stage renal disease, multiple myeloma, solid tumor carcinoma, and myelodysplastic syndrome to be 87%, 79%, 40% and 13%, respectively. An increase in hematocrit of 0.06 or a 20 gram per liter increase in hemoglobin was considered to be a clinical response (Marsh et al., 1999).

Support for using epoetin alfa to treat anemia in patients who have cancer and are undergoing palliative treatment can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors.

Support for using epoetin alfa to increase the capacity for donation for future autologous transfusion prior to elective surgery is supported by several studies. Evidence supports the use of epoetin to prevent anemia in patients who donate blood and to increase the capacity for donation (for future autologous transfusion) prior to elective surgery. The medication has been found to be effective in females, patients with low packed-cell volumes due to anemia or small body size, and patients requiring donation of 4 units or more of blood. Preoperative autologous blood donation with erythropoietin support was beneficial in two studies of abdominal aortic aneurysm (AAA) repair. In a consecutive series (n=20), intravenous erythropoietin 6000 units was administered immediately after withdrawal of one unit of blood (14 days prior to surgery) and again 3 days later, then repeated with the second autologous donation 1 week later (1 week prior to surgery). Subjects also received iron supplementation. The systolic blood pressure decreased to 119 millimeters of mercury following the two blood donations, with no instances of hypertension reported. From before the first blood donation to the time of surgery, hemoglobin declined from 13.8 to 12.4 grams/deciliter, while the reticulocyte count rose significantly. Endogenous erythropoietin levels remained unaffected. While all patients received perioperative autologous transfusions of one to two units, only two patients needed a homologous blood transfusion (Urayama et al., 2000).
In a study of 47 patients by Goodnough et al. (1989), the mean number of units of blood collected per patient in the erythropoietin group was 5.4 +/- 0.2 compared with 4.1 +/- 0.2 in the placebo group. These patients received either erythropoietin in doses of 600 units/kilogram twice weekly for three weeks prior to surgery or

placebo. Patients were excluded if their hematocrits fell below 34%. Of the patients treated with erythropoietin (n=23) only 4% were unable to donate more than 4 units of blood whereas 29% of those patients receiving placebo (n=24) were unable to donate the same number of units.

Use in cancer and related neoplastic conditions is covered according to the conditions outlined in National Coverage Determination Manual section 110.21 (Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions).

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Flolan (epoprostenol injection)
Veletri (epoprostenol injection)
epoprostenol injection

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Flolan/Veletri/epoprostenol is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Compendial Uses
1. Angina pectoris
2. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Pulmonary Hypertension (PH)
Indefinite authorization may be granted for treatment of pulmonary hypertension when ALL of the following criteria are met:
1. The pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left-sided atrial or ventricular disease, left-sided valvular heart disease, etc.) or disorders of the respiratory system (e.g., chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea, or other sleep disordered breathing, alveolar hypoventilation disorders, etc.)
2. The member has primary pulmonary hypertension or pulmonary hypertension, which is secondary to one of the following conditions: connective tissue disease, thromboembolic disease of pulmonary arteries, human immunodeficiency virus (HIV) infection, cirrhosis, diet drugs, congenital left to right shunts, etc. If these conditions are present, then all of the following criteria must be met:
   i. The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition.
   ii. The mean pulmonary artery pressure is greater than 25 mmHg at rest or greater than 30 mmHg with exertion.
   iii. The member has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope).
   iv. Treatment with oral calcium channel blocking agents has been tried and failed or has been considered and ruled out.

B. Angina Pectoris
Authorization of 3 months may be granted for treatment of angina pectoris.

C. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)
Authorization of 12 months may be granted for treatment of peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy).

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit.

A. Pulmonary Arterial Hypertension (PAH)
Authorization for members who are requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. Angina pectoris
Authorization of 3 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat angina pectoris.
3. The member is receiving benefit from therapy. Benefit is defined as either:
   a. Disease stability
   b. Disease improvement

C. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)
Authorization of 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy).
3. The member is receiving benefit from therapy. Benefit is defined as either:
   a. Disease stability
   b. Disease improvement

IV. APPENDIX

WHO Classification of Pulmonary Hypertension

1 PAH
1.1 Idiopathic (PAH)
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4. PAH associated with:
   1.4.1 Connective tissue diseases
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart diseases
   1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders

4 PH due to pulmonary artery obstruction
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
   4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
   4.2.2 Other malignant tumors

Renal carcinoma
Uterine carcinoma
Germ cell tumours of the testis
Other tumours

4.2.3 Non-malignant tumours
Uterine leiomyoma

4.2.4 Arteritis without connective tissue disease

4.2.5 Congenital pulmonary artery stenosis

4.2.6 Parasites
Hydatidosis

5 PH with unclear and/or multifactorial mechanisms

5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders

5.2 Systemic and metabolic disorders: Pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis

5.3 Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis

5.4 Complex congenital heart disease

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Flolan, Veletri and generic epoprostenol.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. External Infusion Pumps Local Coverage Determination (L33794)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Flolan, Veletri and generic epoprostenol are covered in addition to the following:

A. Angina pectoris
B. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information and the external infusion pump Local Coverage Determination (L33794).

Support for using Flolan, Veletri and generic epoprostenol to treat angina pectoris can be found in studies cited in Micromedex. Epoprostenol infusions have been relatively ineffective in patients with exertional angina and unstable angina. In Prinzmetal angina, limited studies suggest lack of beneficial effects in most patients. Support for using epoprostenol for Prinzmetal angina (also known as variant angina) can be found in a small study by Chierchia et al (1982). The study evaluated the effects of IV epoprostenol (PGI2) in nine patients with variant angina and six normal volunteers. In normal subjects, PGI2 (2.5, 5, 10 and 20 nanograms/kg/min) had significant antiplatelet effects, caused a dose-dependent decrease in both systolic and diastolic arterial pressure and a decrease in pulmonary resistance. Heart rate increased in a dose-dependent manner, but no consistent effects on myocardial contractility (evaluated by ultrasound) were observed. Side effects were negligible and readily reversible. Although producing obvious antiplatelet and vasodilatory effects, PGI2 did not affect the number, severity and duration of spontaneous ischemic episodes due to coronary vasospasm in five patients and ergonovine-induced spasm in three. However, the number of ischemic episodes was consistently reduced in one patient during four consecutive periods of PGI2 infusion alternated with placebo. A severe, prolonged ischemic episode with ST elevation and pain was consistently observed in this patient every time PGI2 was discontinued. In the appropriate environment, PGI2 can be administered safely to patients with ischemic heart disease. Occasionally, PGI2 may result in a complete disappearance of ischemic episodes due to coronary vasospasm, but usually it is ineffective. These conflicting results could be related to different etiologies of coronary spasm.

Support for using Flolan, Veletri and generic epoprostenol to treat peripheral vascular disease can be found in small studies. Belch et al (1983) conducted a study of two groups of outpatients with Raynaud's syndrome. The patients were randomly allocated to receive at weekly intervals for three weeks either a 5 h intravenous infusion of buffer or epoprostenol (prostacyclin, PGI2) in buffer (7.5 ng/kg/min after the first hour). PGI2 reduced the frequency and duration of ischemic attacks (both p less than 0.01). Hand temperature measurements with a thermocouple were significantly improved at 1 week; 6 weeks after the last infusion hand temperatures had returned to baseline. There was a corresponding loss of clinical response 8-10 weeks after the last infusion.

Additionally, Bellucci et al (1986) studied infused prostacyclin (PGI2) given IV (7.5 ng/kg/min) three times at weekly intervals in 8 patients with Raynaud's phenomenon (RP). In 4 patients, improvement was long-term, more than 90 days after the last infusion (good responders); in 3 patients, improvement was mild, less than 15 days, and in one patient no improvement was observed (poor responders). Clinical response was always accompanied by improvement, although less prolonged, of capillary appearance and/or function, as judged by microscopy and/or hemodynamic tests (pulse volume index; radial artery blood flow). Lastly, increased catabolism of PGI2 seemed to be excluded in poor responders, since no statistical difference in PGI2 metabolism could be observed between the two groups.

VII. REFERENCES

1. Flolan [package insert]. Durham, NC: GlaxoSmithKline; October 2023
2. Veletri [package insert]. Titusville, NJ: Actelion Pharmaceuticals US, Inc.; July 2022.
3. epoprostenol for Injection [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; January 2021.
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5. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53:1801913; doi:10.1183/13993003.01913-2018.
6. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: 04/04/2023).
7. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132(21):2037-99.
8. Chierchia S, Patrono C, Crea F, et al. Effects of intravenous prostacyclin in variant angina. *Circulation* 1982; 65:470-477.
9. Belch J, Drury JK, Capell H, et a. Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome. A double-blind trial. *Lancet* 1983a; 1:313-315.
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11. External Infusion Pumps (L33794) Version R29. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed October 2, 2023.
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ERBITUX (cetuximab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Squamous Cell Carcinoma of the Head and Neck (SCCHN)
   Erbitux is indicated:
   a. In combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN).
   b. In combination with platinum-based therapy with fluorouracil for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN.
   c. As a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

2. K-Ras Wild-type, EGFR-expressing Colorectal Cancer (CRC)
   Erbitux is indicated for the treatment of *KRAS* wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test:
   a. In combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) for first-line treatment,
   b. In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
   c. As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

   Limitations of Use:
   Erbitux is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

3. BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
   Erbitux is indicated in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

B. Compendial Uses

1. Colorectal cancer
2. Squamous cell carcinoma of the head and neck
3. Occult primary head and neck cancer
4. Gastric and gastroesophageal cancer
5. Non-small cell lung cancer
6. Penile cancer
7. Squamous cell skin cancer

C. CMS Nationally Covered Uses
   The following NCD policy applies to these criteria: Anti-cancer Chemotherapy for Colorectal Cancer (110.17). CMS covers Erbitux for use in specific clinical trials (NCI-CMS Pilot Project). Refer to the Appendix for a list of these covered clinical trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following information must be available, upon request, for all submissions:

A. Documentation of RAS wild-type status or KRAS G12C mutation, where applicable.
B. Documentation of BRAF mutation status, where applicable.
C. Documentation of EGFR expression, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Colorectal Cancer

Authorization of 12 months may be granted for the treatment of colorectal cancer, including appendiceal carcinoma and anal adenocarcinoma, for unresectable/inoperable, advanced, or metastatic disease and the member has not previously experienced clinical failure on panitumumab when either of the following criteria are met:

1. The member meets all of the following criteria:
   i. The RAS (*KRAS and NRAS*) mutation status is negative (wild-type)
   ii. If the tumor is positive for BRAF V600E mutation, the requested medication will be used in combination with encorafenib (Braftovi)
   iii. For colon cancer, the tumor is left-sided only, or
2. The member meets all of the following criteria:
   i. The disease is KRAS G12C mutation positive
   ii. The requested medication will be used in combination with sotorasib (Lumakras) or adagrasib (Krazati)
   iii. The member previously received treatment with chemotherapy

B. Squamous Cell Carcinoma of the Head and Neck Cancer

Authorization of 12 months may be granted for the treatment of squamous cell carcinoma of the head and neck when any of the following criteria is met:

1. Disease is locally or regionally advanced, unresectable, recurrent, persistent, or metastatic.
2. Member is unfit for surgery.
3. The requested medication will be used in combination with radiation.

C. Occult Primary Head and Neck Cancer

Authorization of 12 months may be granted as a single agent or in combination with chemotherapy for treatment of occult primary head and neck cancer for chemoradiation.

D. Penile Cancer

Authorization of 12 months may be granted as a single agent for subsequent treatment of metastatic penile cancer.

E. Gastric and Gastroesophageal Cancer

Authorization of 12 months may be granted for the treatment of locally advanced or metastatic gastric or gastroesophageal cancer.

F. Squamous Cell Skin Cancer

Authorization of 12 months may be granted as a single agent for the treatment of squamous cell skin cancer in unresectable/inoperable/incompletely resected, locally advanced, regional, recurrent, or distant metastatic disease.

G. Non-Small Cell Lung Cancer (NSCLC)

Authorization of 12 months may be granted for subsequent treatment of recurrent, advanced or metastatic NSCLC when all of the following criteria are met:

a. The requested medication will be used in combination with afatinib (Gilotrif).
b. The requested medication will be used in members with a known sensitizing EGFR mutation (e.g., EGFR exon 19 deletion or L858R mutation, or EGFR S768I, L861Q, and/or G719X mutation) following disease progression on EGFR tyrosine kinase inhibitor therapy.

H. Nationally Covered Uses

Authorization of 12 months may be granted for the treatment of patients enrolled in any of the studies listed in the Appendix section.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen and
    ii. No evidence of disease progression while on the current regimen.

V. APPENDIX: Erbitux NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project (Studies in Various Stages of Development)

Study ID #	Study Title	Phase
C80405	Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab, or with the combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum	Phase 3
E2204	An Intergroup Randomized Phase II Study of Bevacizumab or Cetuximab in Combination with Gemcitabine and in Combination with Chemoradiation (Capecitabine and Radiation) in Patients with Completely-Resected Pancreatic Carcinoma	Randomized Phase 2
RTOG-0522	Phase III Trial of Concurrent Accelerated Radiation & Cisplatin vs Concurrent Accelerated Radiation, Cisplatin, & Cetuximab (Followed by Surgery for Selected Patients) for Stage III & IV Head & Neck Carcinomas	Phase 3

Web page with links to the protocol summaries, eligibility and site locations:
https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id90b.pdf

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Erbitux.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Penile cancer
4. NCCN Guideline: Squamous cell skin cancer
5. NCCN Guideline: Colon cancer
6. NCCN Guideline: Head and neck cancers
7. NCCN Guideline: Rectal cancer
8. National Coverage Determination (NCD) for Anti-cancer Chemotherapy for Colorectal Cancer (110.17)
9. NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Erbitux are covered in addition to the following:
1. Colorectal cancer

2. Head and neck cancer
3. Gastric and gastroesophageal cancer
4. Non-small cell lung cancer
5. Penile cancer
6. Squamous cell skin cancer

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Erbitux to treat colorectal cancer, squamous cell carcinoma of the head and neck, occult primary head and neck cancer, non-small cell lung cancer, penile cancer, and squamous cell skin cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Erbitux to treat gastric cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Use of Erbitux in an NCI/CTE-sponsored study is covered according to the conditions outlined in National Coverage Determination Manual section 110.17 Anti-Cancer Chemotherapy for Colorectal Cancer.

VIII. REFERENCES

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HALAVEN (eribulin mesylate)
eribulin mesylate

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.
   2. Treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

B. Compendial Uses
   1. Breast cancer
   2. Soft tissue sarcoma
      a. Retroperitoneal/intra-abdominal soft tissue sarcoma
      b. Pleomorphic rhabdomyosarcoma
      c. Extremity/body wall, head/neck

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: human epidermal growth factor receptor 2 (HER2) status testing results (where applicable).

III. CRITERIA FOR INITIAL APPROVAL

A. Breast Cancer

Authorization of 12 months may be granted for treatment of recurrent or metastatic breast cancer or breast cancer with no response to preoperative systemic therapy when any of the following criteria is met:
1. The requested medication will be used as a single agent for HER2-negative disease; or
2. The requested medication will be used in combination with margetuximab-cmkb or trastuzumab for HER2-positive disease.

B. Soft Tissue Sarcoma

Authorization of 12 months may be granted for treatment of any of the following types of soft tissue sarcoma, as single-agent therapy:
1. Liposarcoma
2. Pleomorphic rhabdomyosarcoma
3. Retroperitoneal/intra-abdominal soft tissue sarcoma
4. Extremity/ body wall, head/neck

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section III when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Halaven and eribulin mesylate.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Breast Cancer
4. NCCN Guideline: Soft Tissue Sarcoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Halaven and eribulin mesylate are covered in addition to breast cancer and soft tissue sarcoma.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using eribulin mesylate to treat breast cancer and soft tissue sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Halaven [package insert]. Nutley, NJ: Eisai Inc.; September 2022.
2. Eribulin mesylate [package insert]. Weston, FL: Apotex Corp.; February 2024.
3. The NCCN Drugs & Biologics Compendium 2022 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 2023.

EVENITY (romosozumab-aqqg)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Evenity is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

Limitations of Use: Limit duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Postmenopausal osteoporosis treatment
Authorization of a total of 12 months may be granted for treatment of postmenopausal osteoporosis in members who are at high risk for fracture.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for a total of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Evenity
B. Evenity is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy.
D. The member has not yet received 12 months of therapy with Evenity.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Evenity.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis
4. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Evenity are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the use of Evenity in postmenopausal women with osteoporosis can be found in the guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinology. Evenity, in addition to abaloparatide, denosumab, teriparatide and zoledronate, should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk. Treatment with Evenity should be limited to one year and treatment followed with a drug intended for long-term use (bisphosphonate, denosumab).

Support for the use of Evenity in postmenopausal women with osteoporosis can be found in the Endocrine Society guideline "Pharmacological Management of Osteoporosis in Postmenopausal Women". The guideline recommends Evenity therapy in postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis (i.e., low T-score < −2.5 and fractures) or multiple vertebral fractures. The guideline recommends treatment for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures. The recommended dosage is 210 mg monthly by subcutaneous injection for 12 months. Women at high risk of cardiovascular disease and stroke should not be considered for Evenity pending further studies on cardiovascular risk associated with this treatment. High risk includes prior myocardial infarction or stroke. In postmenopausal women with osteoporosis who have completed a course of Evenity, the guidelines recommend treatment with antiresorptive osteoporosis therapies to maintain bone mineral density gains and reduce fracture risk.

VI. REFERENCES

1. Evenity [package insert]. Thousand Oaks, CA: Amgen; April 2020.
2. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105(3):587-594.
3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract*. 2020;26(suppl 1):1-46.

EVKEEZA (evinacumab-dgnb)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Evkeeza is indicated as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 5 years and older, with homozygous familial hypercholesterolemia (HoFH).

Limitations of Use:
- The safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).
- The effects of Evkeeza on cardiovascular morbidity and mortality have not been determined.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Genetic testing or medical records confirming the diagnosis of HoFH.
B. LDL-C level dated within the six months preceding the authorization request.
C. For members 10 years of age and older: chart notes, medical record documentation, or claims history confirming the member is currently on maximally tolerated lipid-lowering therapy.
D. For members 7 years of age to less than 10 years of age: chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

III. CRITERIA FOR INITIAL APPROVAL

Homozygous familial hypercholesterolemia (HoFH)
Authorization of 6 months may be granted for members 5 years of age and older for the treatment of homozygous familial hypercholesterolemia when both of the following criteria are met:
A. Member has a documented diagnosis of homozygous familial hypercholesterolemia confirmed by any of the following criteria:
    1. Variant in two low-density lipoprotein receptor (LDLR) alleles.
    2. Presence of homozygous or compound heterozygous variants in apolipoprotein B (APOB) or proprotein convertase subtilisin-kexin type 9 (PCSK9).
    3. Member has compound heterozygosity or homozygosity for variants in the gene encoding low-density lipoprotein receptor adaptor protein 1 (LDLRAP1).
    4. An untreated LDL-C of greater than 400 mg/dL and either of the following:
        a. Presence of cutaneous or tendinous xanthomas before the age of 10 years.
        b. An untreated LDL-C level of greater than or equal to 190 mg/dL in both parents.
B. Prior to initiation of treatment with the requested medication, both of the following criteria are/were met:
    1. Member has a treated LDL-C of greater than or equal to 100 mg/dL (or greater than or equal to 70 mg/dL with clinical atherosclerotic cardiovascular disease [ASCVD])
    2. Member meets one of the following:
        a. Member is 10 years of age or older and meets both of the following:

i. Member is receiving stable treatment with at least 2 lipid-lowering therapies (e.g., statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 [PCSK9] directed therapy) at the maximally tolerated dose.
ii. Member will continue to receive concomitant lipid-lowering therapy at the maximally tolerated dose.

b. Member is 7 years of age to less than 10 years of age and meets either of the following:
i. Member is receiving stable treatment with at least one lipid-lowering therapy (e.g., statins, LDL apheresis) at the maximally tolerated dose and will continue to receive concomitant lipid-lowering therapy at the maximally tolerated dose.
ii. Member has an intolerance or contraindication to other lipid-lowering therapies.

c. Member is 5 years of age to less than 7 years of age.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Evkeeza.
B. Evkeeza is being used to treat an indication enumerated in Section III.
C. Member meets one of the following:
1. Member is 10 years of age or older and is currently receiving concomitant lipid-lowering therapy at the maximally tolerated dose.
2. Member is 7 years of age to less than 10 years of age and meets either of the following:
a. Member is currently receiving concomitant lipid-lowering therapy at the maximally tolerated dose.
b. Member has an intolerance or contraindication to other lipid-lowering therapies.
3. Member is 5 years of age to less than 7 years of age.
D. The member is receiving benefit from therapy. Benefit is defined as either of the following:
1. LDL-C is now at goal.
2. Member has had at least a 30% reduction of LDL-C from baseline.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Evkeeza.
2. The available compendium
a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology
3. Update on European atherosclerosis society consensus statement on homozygous familial hypercholesterolaemia: new treatments and clinical guidance.
4. National Lipid Association recommendations for patient-centered management of dyslipidemia.
5. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
6. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia from the American Heart Association.
7. 2022 American College of Cardiology Expert Consensus Decision Pathway on the Role of Nonstatin therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Evkeeza are included.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the inclusion criteria for the ELIPSE HoFH trial. If the patient does not have the any of the above-mentioned genetic mutations, it is possible to approve the drug based on the patient's untreated LDL-C level. According to the guidelines published by the European Atherosclerosis Society, the diagnosis of HoFH can be assumed if the patient has an untreated LDL-C greater than 400 mg/dL and has a history of cutaneous or tendinous xanthomas before the age of 10. Alternatively, if both parents have an untreated LDL-C of at least 190 mg/dL, then the diagnosis of HoFH can also be assumed.

Currently, there is not a statin marketed in the United States FDA-approved for children under the age of seven, therefore for children between the ages of five and seven, there is no requirement for prior pharmacotherapy.

VII. REFERENCES

1. Evkeeza [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals Inc.; March 2023.
2. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med.* 2020;383:711-20.
3. Cuchel M, Raal FJ, Hegele RA, et al. Update on European atherosclerosis society consensus statement on homozygous familial hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277-2291.
4. Grundy SM, Stone NJ, Bailey, AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082– e1143.
5. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, et al. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc*. 2019;8(24):e013225.
6. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Evaluate the efficacy and safety of evinacumab in pediatric patients With homozygous familial hypercholesterolemia. Identifier: NCT04233918. Updated June 7, 2023. Accessed November 13, 2023. https://clinicaltrials.gov/ct2/show/record/NCT04233918.
7. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the American college of cardiologic solution set oversight committee. *J Am Coll Cardiol.* 2022;80(14):1366–1418.

EXONDYS 51 (eteplirsen)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Exondys 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 51 skipping (refer to examples in Appendix).
B. Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD).

IV. CRITERIA FOR INITIAL APPROVAL

Duchenne Muscular Dystrophy
Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:
A. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
B. The DMD gene mutation is amenable to exon 51 skipping (refer to examples in Appendix).
C. Treatment with Exondys 51 is initiated before the age of 14.
D. Member is able to achieve an average distance of at least 180 meters while walking independently over 6 minutes.
E. Member will not exceed a dose of 30 mg/kg once weekly.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with Exondys 51.
B. Exondys 51 is being used to treat an indication enumerated in Section IV.
C. The member is receiving benefit from therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent).
D. The member will not exceed a dose of 30 mg/kg once weekly.

VI. APPENDIX

Examples of DMD gene mutations (exon deletions) amenable to exon 51 skipping (not an all-inclusive list):

1. Deletion of exon 50
2. Deletion of exon 52
3. Deletion of exons 45-50
4. Deletion of exons 47-50
5. Deletion of exons 48-50
6. Deletion of exons 49-50

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Exondys 51.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Exondys 51 are covered.

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

IX. REFERENCES

1. Exondys 51 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; January 2022.
2. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74(5):637-47.
3. Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *Lancet*. 2011;378(9791):595-605.
4. Mendell JR, Goemans N, Lowes LP, et al; Eteplirsen Study Group and Telethon Foundation DMD Italian Network. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. 2016;79(2):257-271.
5. Randeree L, Eslick GD. Eteplirsen for paediatric patients with Duchenne muscular dystrophy: A pooled-analysis. J Clin Neurosci. 2018;49:1-6.

EYLEA (aflibercept)
EYLEA HD (aflibercept)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Eylea is indicated for the treatment of:
A. Neovascular (wet) age-related macular degeneration
B. Macular edema following retinal vein occlusion
C. Diabetic macular edema
D. Diabetic retinopathy
E. Retinopathy of Prematurity

Eylea HD is indicated for the treatment of:
A. Diabetic macular edema
B. Diabetic retinopathy
C. Neovascular (wet) age-related macular degeneration

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Neovascular (wet) age-related macular degeneration
Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

B. Macular edema following retinal vein occlusion
Authorization of 12 months may be granted for treatment of macular edema following retinal vein occlusion.

C. Diabetic macular edema
Authorization of 12 months may be granted for the treatment of diabetic macular edema.

D. Diabetic retinopathy
Authorization of 12 months may be granted for the treatment of diabetic retinopathy.

E. Retinopathy of Prematurity
Authorization of 12 months may be granted for the treatment of retinopathy of prematurity.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when ALL of the following criteria are met:
A. The member is currently receiving therapy with Eylea.
B. Eylea is being used to treat an indication enumerated in Section II.
C. The medication has been effective for treating the diagnosis or condition.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Eylea
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Eylea are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCE

1. Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals Inc.; February 2023.
2. Eylea HD [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals; August 2023

FABRAZYME (agalsidase beta)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Fabrazyme is indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: alpha-galactosidase enzyme assay or genetic testing results supporting diagnosis. In the case of obligate carriers, the documentation must be submitted for the parent.
B. Continuation requests: lab results or chart notes documenting a benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

Fabry disease
Authorization of 12 months may be granted for treatment of Fabry disease when the diagnosis of Fabry disease was confirmed by enzyme assay demonstrating a deficiency of alpha-galactosidase enzyme activity or by genetic testing, or the member is a symptomatic obligate carrier.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy (e.g., reduction in plasma globotriaosylceramide [GL-3] or GL-3 inclusions, improvement and/or stabilization in renal function, pain reduction).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Fabrazyme.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document.
4. Fabry disease revisited: Management and treatment recommendations for adult patients.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Fabrazyme are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The diagnosis of Fabry disease can be confirmed using several methods. According to Biegstraaten et al, a definite diagnosis of Fabry disease is made when the patient has a GLA mutation, deficiency of alpha-galactosidase enzyme activity in leukocytes and one of the following: one or more characteristic sign of Fabry disease (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma), an increase in plasma (lyso)Gb3, or a family member with a definite Fabry disease diagnosis carrying the same GLA mutation. Additionally, Ortiz et al report a larger group of patients have later-onset phenotypes and varying levels of residual alpha-galactosidase enzyme activity. Severe clinical manifestations have been reported in at least 43% of obligate carrier women. Enzyme replacement therapy should be considered in these cases if there is laboratory, histological, or imaging evidence of injury to the kidney, heart or central nervous system regardless of the alpha-galactosidase enzyme activity.

VII. REFERENCES

1. Fabrazyme [package insert]. Cambridge, MA: Genzyme Corporation; March 2021.
2. Biegstraaten M, Arngrimsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet J Rare Dis.* 2015; 1036.
3. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123(4):416-427.

REBINYN (coagulation factor IX [recombinant], glycoPEGylated)
IDELVION (coagulation factor IX [recombinant], albumin fusion protein)
ALPROLIX (coagulation factor IX [recombinant], Fc fusion protein)
BENEFIX, IXINITY, RIXUBIS (coagulation factor IX [recombinant])
ALPHANINE SD (coagulation factor IX [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Hemophilia B

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Hemophilia B
Authorization of 12 months may be granted for treatment of hemophilia B.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds)

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for the factor IX products (Rebinyn, Idelvion, Alprolix, BeneFIX, Ixinity, Rixubis, AlphaNine SD).
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the factor IX products are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Alprolix [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; May 2023.
2. BeneFIX [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals LLC; November 2022.
3. Ixinity [package insert]. Chicago, IL: Medexus Pharma, Inc.; November 2022.
4. Rixubis [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2023.
5. AlphaNine SD [package insert]. Los Angeles, CA: Grifols Biologicals LLC; November 2022.
6. Idelvion [package insert]. Kankakee, IL: CSL Behring LLC; June 2023.
7. Rebinyn [package insert]. DK-2880 Bagsvaerd, Denmark: Novo Nordisk A/S; August 2022.
8. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
9. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 5, 2023.

PROFILNINE (factor IX complex [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Hemophilia B

B. Compendial Uses
1. Bleeding due to low levels of liver-dependent coagulation factors
2. Factor II deficiency
3. Factor X deficiency
4. Anticoagulation reversal

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Hemophilia B
Authorization of 12 months may be granted for treatment of hemophilia B.

B. Bleeding due to low levels of liver-dependent coagulation factors
Authorization of 12 months may be granted for treatment of bleeding due to low levels of liver-dependent coagulation factors.

C. Factor II deficiency
Authorization of 12 months may be granted for treatment of factor II deficiency.

D. Factor X deficiency
Authorization of 12 months may be granted for treatment of factor X deficiency.

E. Anticoagulation reversal
Authorization of 1 month may be granted for anticoagulation reversal.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Anticoagulation Reversal
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. All Other Indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Profilnine.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Profilnine are covered in addition to the following:

1. Bleeding due to low levels of liver-dependent coagulation factors
2. Factor II deficiency
3. Factor X deficiency
4. Anticoagulation reversal

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Profilnine to treat bleeding due to low levels of liver-dependent coagulation factors can be found in a study of 30 patients by Gazzard and colleagues. Factor IX was at least as effective as fresh frozen plasma in the treatment of clotting factor deficiency secondary to severe liver disease. In a comparison of the two agents in 30 patients with chronic liver disease, all patients had prothrombin times that were prolonged 4 seconds or more and were to undergo percutaneous needle liver biopsy. The first 15 patients were given 600 mL fresh frozen plasma over 30 minutes, followed by 300 mL 6 hours later. The second 15 patients were given 20 mL of factor IX complex containing 2000 units of factors II, IX, and X. Vital signs and signs of bleeding were monitored for 24 hours post-biopsy; packed cell volume and coagulation studies were performed. Although there was no evidence of bleeding in any patient, only 3 of 15 patients receiving fresh frozen plasma had a normal prothrombin time after biopsy, and in 7 of the 15 patients receiving factor IX, the prothrombin time was within normal limits 30 minutes after receiving the dose. Serum levels of clotting factors increased to above 10% of normal in all 30 patients, and were still increased 24 hours post-dosing. No thrombotic sequelae were reported.

Support for using Profilnine to treat factor II deficiency can be found in the guideline posted by the National Bleeding Disorders Foundation. Profilnine is a human plasma-derived prothrombin complex concentrate recommended for use in patients with factor II deficiency.

Support for using Profilnine to treat factor X deficiency can be found in a case report by Kouides and Kulzer. An 18-year-old male with severe factor X deficiency (level less than 1%) successfully used home-infusion prophylactic treatment with factor IX (Profilnine(R)) to overcome epistaxis and joint bleeding. Prior to initiation of the prophylactic regimen, the patient was treated on demand from 3 to 14 times a year. Nose bleeds were most common, followed by joint bleeds and hematomas (the result of trauma). His factor IX protocol was 30 units/kg twice a week at least 3 days apart. If breakthrough bleeding occurred, he was to infuse another dose. He was instructed not to infuse more than 2 doses in 24 hours or to receive infusions on more than 3 consecutive days. During the initial 12 months of prophylactic therapy, no breakthrough bleeding occurred. During an additional 11 months of therapy, he reported one bleeding episode that was the result of trauma. His quality of life improved after starting this protocol. He had no absences from school due to bleeding; he was able to participate in recreational basketball and track. No thrombotic events occurred. A trough level measured at 48 hours after factor IX infusion showed a factor X level of 30% (minimum hemostatic level 10% to 20%). Additionally, support can be found in the guideline posted by the National Bleeding Disorders Foundation. Profilnine is a human plasma-derived prothrombin complex concentrate recommended for use in patients with factor X deficiency.

Support for using Profilnine to treat drug toxicity due to anticoagulant can be found in a retrospective chart review by Safaoui et al. A retrospective chart review revealed that Factor IX complex in combination with traditional therapy achieved rapid reversal of warfarin-induced coagulopathy in patients with intracranial hemorrhage (n=28). Adult patients (mean age 78.2 years (yr); range, 55 to 94 yr; 50% male) were divided into 1 of 2 groups based on the time from presentation to administration of Factor IX complex, 60 minutes or less (group 1) or more than 60 minutes (group 2). All patients received Factor IX complex 2000 units. Patients with an INR greater than 3 at 10 minutes after Factor IX complex infusion received a repeat dose. Vitamin K 10 mg IV or subQ was administered to 82% (23 of 28) of patients and 96% (27 of 28) of patients received fresh frozen plasma. The mean INR at presentation for group 1 was 5.8 +/- 8.6, which significantly reduced to 2.2 +/- 0.76 (p=0.005) after treatment. Similarly, the mean INR at presentation for group 2 was 4.7 +/- 3.2, which significantly reduced to 1.8 +/- 0.73 (p=0.001) after treatment. Of 11 patients with an INR obtained within 30 minutes of Factor IX complex infusion, the mean time to INR correction was 13.5 minutes (min). For all patients, the mean time to INR correction was 116 min. At 24 hours, reversal of warfarin-induced coagulopathy remained significant 1.8 +/- 0.87 (p=0.012) and 1.2 +/- 0.28 (p=0.001) in group 1 and 2, respectively. No early thrombotic or allergic events were reported. Fatalities occurred in 10 patients designated as do not resuscitate. Additionally, a retrospective chart review by Siddiq and colleagues found factor IX complex concentrate in combination with fresh frozen plasma and vitamin K (n=10) may be a more effective alternative than fresh frozen plasma (FFP) and vitamin K alone (n=9) for rapid reversal of warfarin-induced coagulopathy in patients with intracranial hemorrhage. Consecutive patients received either Factor IX complex concentrate 25 units/kg (INR less than 4) or 50 units/kg (INR greater than 4) IV push over 2 to 5 minutes in combination with vitamin K 10 mg IV infusion over 30 minutes and FFP 10 to 15 mL/kg (age 67.2 +/- 18.51 years (yr); 50% male) or FFP and vitamin K alone (76.89 +/- 18.5 yr; 56% male). INR was monitored upon presentation and approximately every 3 hours (hr) thereafter until a target INR of 1.4 or less was met. The mean INR at presentation was 2.44 +/- 1.48 for the Factor IX complex concentrate group and 1.84 +/- 0.31 for the FFP-vitamin K alone group. Both treatments significantly reduced INR to target level. The mean INR was reduced to 1.34 +/- 0.07 (p less than 0.005) in the Factor IX complex concentrate group and 1.34 +/- 0.08 (p less than 0.05) in the FFP-vitamin K alone group. However, 80% of patients (8 of 10) met the target INR within 3 to 4 hr of treatment initiation in the Factor IX complex concentrate group compared with 33% (3 of 9) in the FFP-vitamin K alone group (p=0.012). The mean time required to correct INR was significantly less in the Factor IX complex concentrate group 4.25 +/- 2.12 hr compared with the FFP-vitamin K alone group 8.52 +/- 5.6 hr (p less than 0.05). No treatment complications were observed.

VI. REFERENCES

1. Profilnine [package insert]. Los Angeles, CA: Grifols Biologicals LLC; June 2023.
2. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically www.micromedexsolutions.com [available with subscription]. Accessed December 5, 2023.
3. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 5, 2023.
4. Gazzard BG, Henderson JM, & Williams R: The use of fresh frozen plasma or a concentrate of factor IX as replacement therapy before liver biopsy. Gut 1975; 16:621-625.
5. Kouides PA & Kulzer L: Prophylactic treatment of severe factor X deficiency with prothrombin complex concentrate. Haemophilia 2001; 7:220-223.
6. Safaoui MN, Aazami R, Hotz H, et al: A promising new alternative for the rapid reversal of warfarin coagulopathy in traumatic intracranial hemorrhage. Am J Surg 2009; 197(6):785-790.
7. Siddiq F, Jalil A, McDaniel C, et al: Effectiveness of Factor IX complex concentrate in reversing warfarin associated coagulopathy for intracerebral hemorrhage. Neurocrit Care 2008; 8(1):36-41.

FACTOR VIII CONCENTRATES

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

Table: Factor VIII Concentrates and Covered Uses

Brand	Generic	FDA-Approved Indication(s)	Compendial Indication(s)
Recombinant Factor VIII Concentrates			
Advate	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Afstyla	antihemophilic factor [recombinant], single chain	Hemophilia A	
Kogenate FS	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Kovaltry	antihemophilic factor [recombinant]	Hemophilia A	
Novoeight	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Nuwiq	antihemophilic factor [recombinant]	Hemophilia A	
Recombinate	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Xyntha	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Extended Half-life Recombinant Factor VIII Concentrates			
Adynovate	antihemophilic factor [recombinant], PEGylated	Hemophilia A	
Altuviiio	antihemophilic factor [recombinant], Fc-VWF-XTEN fusion protein-ehtl	Hemophilia A	
Eloctate	antihemophilic factor [recombinant], Fc fusion protein	Hemophilia A	
Jivi	antihemophilic factor [recombinant], PEGylated-aucl	Hemophilia A	
Esperoct	antihemophilic factor [recombinant], Glycopegylated-exei	Hemophilia A	
Human Plasma-Derived Factor VIII Concentrate			
Hemofil M	antihemophilic factor [human] monoclonal antibody purified	Hemophilia A	Acquired Hemophilia A
Human Plasma-Derived Factor VIII Concentrates That Contain Von Willebrand Factor			
Alphanate **Humate-P**	antihemophilic factor/von Willebrand factor complex [human]	Hemophilia A, von Willebrand Disease	Acquired Hemophilia A, Acquired von Willebrand Syndrome
Koate	antihemophilic factor [human]	Hemophilia A	Acquired Hemophilia A, von Willebrand Disease

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Hemophilia A

Authorization of 12 months of Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, or Xyntha may be granted for treatment of hemophilia A when either of the following criteria is met:

1. Member has mild disease (see Appendix A) and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
2. Member has moderate or severe disease (see Appendix A).

Authorization of 12 months of Jivi may be granted for treatment of hemophilia A when BOTH of the following criteria are met:

1. Member has previously received treatment for hemophilia A with a factor VIII product.
2. Member is ≥ 12 years of age.

B. Von Willebrand Disease (VWD)

Authorization of 12 months of Alphanate, Humate-P, or Koate may be granted for treatment of VWD when any of the following criteria is met:

1. Member has type 1, 2A, 2M, or 2N VWD and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
2. Member has type 2B or type 3 VWD.

C. Acquired Hemophilia A

Authorization of 12 months of Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, or Xyntha may be granted for treatment of acquired hemophilia A.

D. Acquired von Willebrand Syndrome

Authorization of 12 months of Alphanate or Humate-P may be granted for treatment of acquired von Willebrand syndrome.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix A: Classification of Hemophilia by Clotting Factor Level (% Activity) and Bleeding Episodes

Severity	Clotting Factor Level % activity*	Bleeding Episodes
Severe	<1%	Spontaneous bleeding episodes, predominantly into joints and muscles Severe bleeding with trauma, injury or surgery
Moderate	1% to 5%	Occasional spontaneous bleeding episodes Severe bleeding with trauma, injury or surgery
Mild	6% to 40%	Severe bleeding with serious injury, trauma or surgery

*Factor assay levels are required to determine the diagnosis and are of value in monitoring treatment response.

Appendix B: Clinical Reasons For Not Utilizing Desmopressin in Patients with Hemophilia A and Type 1, 2A, 2M and 2N VWD

A. Age < 2 years

B. Pregnancy
C. Fluid/electrolyte imbalance
D. High risk for cardiovascular or cerebrovascular disease (especially the elderly)
E. Predisposition to thrombus formation
F. Trauma requiring surgery
G. Life-threatening bleed
H. Contraindication or intolerance to desmopressin
I. Severe type 1 von Willebrand disease
J. Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for the factor VIII agents listed in section I.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007
4. Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update.
5. WFH Guidelines for the Management of Hemophilia, 3rd edition.
6. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.
7. MASAC recommendations regarding the treatment of von Willebrand disease.
8. Acquired hemophilia. World Federation of Hemophilia.
9. International recommendations on the diagnosis and treatment of acquired hemophilia A.
10. Acquired haemophilia A: a 2013 update.
11. National Hemophilia Foundation. Hemophilia A (Factor VIII Deficiency).
12. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the factor VIII agents listed in section I are covered in addition to the following:

A. Acquired hemophilia A for Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, Xyntha
B. Acquired von Willebrand syndrome for Alphanate and Humate-P
C. Von Willebrand disease for Koate

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate and Xyntha to treat mild hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Mild disease is defined as having a clotting factor level of 6 to 40% of normal. The patient generally experiences severe bleeding with major trauma or surgery. It is rare these patients will bleed spontaneously. Desmopressin may be the treatment of choice for patients with mild hemophilia A when factor VIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using clotting factor concentrates. Desmopressin is not appropriate in all situations. Patients under 2 years of age, pregnant patients, patients with electrolytes or fluid imbalance, patients at high risk for cerebrovascular disease, predisposition to thrombus formation, patients who experienced trauma severe enough to require surgery, and patients experiencing a life-threatening bleed are not ideal candidates for desmopressin therapy.

Support for using Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate and Xyntha to treat moderate to severe hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Patients with moderate to severe hemophilia A should be started on prophylaxis with factor VIII or a non-factor therapy like Hemlibra to prevent a recurring life-threatening bleed. Desmopressin is not appropriate in these patients.

Support for using Alphanate, Humate-P, and Koate to treat von Willebrand syndrome can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". Humate-P and Alphanate are approved by the FDA to treat von Willebrand syndrome. Koate has been used off-label for this use as well. Regarding the use of desmopressin, Type 2B and type 3 VWD does not respond consistently to desmopressin therapy and therefore desmopressin is not considered clinically useful in these patients.

Support for using Advate, Kogenate FS, Novoeight, Recombinate, and Xyntha to treat acquired hemophilia A can be found in the AHFS-DI database maintained by the American Society of Health System Pharmacists. Antihemophilic factor (recombinant) has been used in the management of bleeding episodes in some patients with acquired hemophilia A who have low levels of inhibitors. Although antihemophilic factor therapy may be effective in some patients with low levels of acquired antihemophilic factor inhibitors when given in high doses current evidence indicates that bypassing agents are substantially more effective in achieving hemostatic control and are considered the treatment of choice in patients with this condition.

Support for using Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, and Xyntha to treat acquired hemophilia A can be found in the international recommendations on the diagnosis and treatment of acquired hemophilia A (Tiede et al, 2020). Human (plasma-derived or recombinant) factor VIII is recommended if recombinant factor VIIa, activated prothrombin complex concentrate and recombinant porcine factor VIII is unavailable, and the inhibitor titer is low.

Support for using Alphanate and Humate-P to treat acquired von Willebrand syndrome can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". The guideline indicates DDAVP and VWF/FVIII concentrates are first line therapy. If a patient has an inadequate response to DDAVP and VWF/FVIII concentrates, intravenous immunoglobulin given alone was effective in controlling bleeding and raising VWF:RCo activity.

IV. REFERENCES

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7. Novoeight [package insert]. Plainsboro, NJ: Novo Nordisk Inc., July 2020.
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FASENRA (benralizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Fasenra is indicated for the add-on maintenance treatment of patients aged 6 years and older with severe asthma, and with an eosinophilic phenotype.

Limitations of Use:

- *Not for treatment of other eosinophilic conditions*
- *Not for relief of acute bronchospasm or status asthmaticus*

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. For initial requests:
   1. Chart notes or medical record documentation showing baseline blood eosinophil count.
   2. Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, then clinical reason to avoid therapy.
B. For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

Eosinophilic asthma
Authorization of 12 months may be granted for treatment of eosinophilic asthma when all of the following criteria are met:

A. Member is 6 years of age or older.
B. Member has a baseline blood eosinophil count (pre-treatment with a biologic indicated for asthma) of at least 150 cells per microliter.
C. Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
   1. Inhaled corticosteroid
   2. Additional controller (i.e., long-acting beta$_2$-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline)
D. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Nucala, Tezspire, Xolair).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months may be granted when all of the following criteria are met:

A. Member is 6 years of age or older.

B. The member is currently receiving therapy with the requested medication.
C. The requested medication is being used to treat an indication enumerated in Section III.
D. The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.
E. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Nucala, Tezspire, Xolair).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Fasenra.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023 update.
4. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Fasenra are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Fasenra to treat severe asthma can be found in the Global Initiative for Asthma (GINA) guidelines. For adults and adolescents, anti-IL5 receptor antagonist can be a drug used when either medium dose maintenance inhaled corticosteroids with formoterol or medium to high dose maintenance inhaled corticosteroids with long-acting beta$_2$-agonists are not controlling the patient's asthma.

VII. REFERENCES

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FEIBA (anti-inhibitor coagulant complex [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Hemophilia A and hemophilia B with inhibitors

B. Compendial Use
Acquired hemophilia A

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Hemophilia A with Inhibitors
Authorization of 12 months may be granted for treatment of hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or if the member has a history of an inhibitor titer ≥ 5 BU.

B. Hemophilia B with Inhibitors
Authorization of 12 months may be granted for treatment of hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or if the member has a history of an inhibitor titer ≥ 5 BU.

C. Acquired Hemophilia A
Authorization of 12 months may be granted for treatment of acquired hemophilia A.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. APPENDIX

Appendix: Inhibitors - Bethesda Units (BU)
The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for FEIBA.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. International recommendations on the diagnosis and treatment of acquired hemophilia A.
4. Acquired haemophilia A: a 2013 update.
5. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.
6. World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, 3rd edition.
7. MASAC Recommendations Regarding Prophylaxis with Bypassing Agents in Patients with Hemophilia and High Titer Inhibitors.
8. Acquired hemophilia A: Updated review of evidence and treatment guidance.
9. National Coverage Determination: Anti-Inhibitor Coagulant Complex (AICC).

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for FEIBA are covered in addition to acquired hemophilia A.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using FEIBA to treat acquired hemophilia A can be found in several guidelines.
The World Federation of Hemophilia supports using activated prothrombin complex concentrate (such as FEIBA) to treat bleeding episodes.
The International Recommendations on the Diagnosis and Treatment of Acquired Hemophilia A recommends recombinant activated factor VII (NovoSeven) and activated prothrombin concentrate complex. The guideline does not recommend one drug over another for the treatment for acute bleeds.

Treatment of hemophilia in patients with factor VIII inhibitor antibodies is covered according to the conditions outlined in National Coverage Determination Manual section Anti-Inhibitor Coagulant Complex (110.3).

VII. REFERENCES

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FENSOLVI (leuprolide acetate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Fensolvi is indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty (CPP).

B. Compendial Uses
Gender dysphoria (also known as transgender and gender diverse (TGD) persons)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all initial requests for central precocious puberty: laboratory report or medical record of a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay.

III. CRITERIA FOR INITIAL APPROVAL

A. Central precocious puberty (CPP)

1. Authorization of 12 months may be granted for treatment of CPP in a female member when all of the following criteria are met:
   i. Member has been evaluated for intracranial tumors (e.g., lab tests, computed tomography [CT] scan, magnetic resonance imaging [MRI]).
   ii. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay.
   iii. The assessment of bone age versus chronological age supports the diagnosis of CPP.
   iv. The member was less than 8 years of age at the onset of secondary sexual characteristics.
2. Authorization of 12 months may be granted for treatment of CPP in a male member when all of the following criteria are met:
   i. Member has been evaluated for intracranial tumors (e.g., lab tests, CT scan, MRI).
   ii. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third-generation LH assay.
   iii. The assessment of bone age versus chronological age supports the diagnosis of CPP.
   iv. The member was less than 9 years of age at the onset of secondary sexual characteristics.

B. Gender dysphoria

1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   i. The member has a diagnosis of gender dysphoria.
   ii. The member has reached Tanner stage 2 of puberty or greater.
2. Authorization of 12 months may be granted for gender transition when all of the following criteria are met:
   i. The member has a diagnosis of gender dysphoria.

ii. The member will receive the requested medication concomitantly with gender-affirming hormones.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat central precocious puberty (CPP).
   3. The member is either a female less than 12 years of age or a male less than 13 years of age.
   4. The member is receiving benefit from therapy. Benefit is defined as the member is not experiencing treatment failure defined as:
      i. Clinical pubertal progression.
      ii. Lack of growth deceleration.
      iii. Continued excessive bone age advancement.

B. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat gender dysphoria.
   3. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Fensolvi.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. Consensus statement on the use of gonadotropin-releasing hormone analogs in children
4. Use of gonadotropin-releasing hormone analogs in children: Update by an international consortium.
5. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline
6. Gender Identity Research and Education Society. Guidance for GPs and other clinicians on the treatment of gender variant people.
7. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, 8th version.
8. Diagnosis and management of precocious sexual maturation: an updated review.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Fensolvi are covered in addition to gender dysphoria.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Fensolvi to treat central precocious puberty (CPP) can be found in guidelines by Bangalore et al. (2019). Luteinizing hormone (LH) is the best biochemical parameter for diagnosing CPP. Randomly obtained serum LH concentrations within the pubertal range confirm the diagnosis of CPP. In the setting of clinically progressive puberty, LH concentrations below the pubertal range do not exclude CPP, suggesting the need for gonadotropin hormone-releasing hormone (GnRH) or GnRHa stimulation testing. In children

diagnosed with CPP, magnetic resonance imaging (MRI) or other diagnostic imaging should be performed in all boys and at least in all girls who are six years or younger to exclude intracranial pathology.
Girls younger than 7 years and boys younger than 9 years showing progressive central puberty, or who are more advanced in pubertal development (e.g., sexual maturation rating (SMR) 3 breast or genital development) with rapid linear growth merit GnRHa treatment. For girls older than 7 years with SMR 2 breast development, an observation period of four to six months is suggested to assess the tempo of pubertal progression before offering treatment. Regarding the cessation of therapy, using GnRHa after achieving a bone age of 12.5 years in girls and 14 years in boys is unlikely to result in significant increase in height. Separately, Kaplowitz et al. (2016) support generally using age 8 in girls as a cut off for secondary sexual characteristics and age 9 in boys. The authors stress that differences between ethnicities and races should be considered when determining if a patient should be sent to a specialist for evaluation for CPP.

Support for using Fensolvi for gender dysphoria can be found in the Endocrine Society Clinical Practice guideline for Endocrine Treatment of gender-dysphoric/gender-incongruent persons. The guidelines support GnRH agonist use in both transgender males and transgender females. Specific products are not listed; therefore, coverage is applied to the entire class of GnRH agonists.
Support for using Fensolvi for gender dysphoria can also be found in the World Professional Association for Transgender Health (WPATH). According to the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, prescribing GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (defined as past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy. PATH also recommends beginning pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

WPATH recommends health care professionals prescribe progestins or a GnRH agonist for eligible transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.
WPATH also recommends health care professionals prescribe testosterone-lowering medications (including GnRH agonists) for eligible transgender and gender diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.

VII. REFERENCES

1. Fensolvi [package insert]. Fort Collins, CO: Tolmar, Inc.; November 2022.
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3. Carel J, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;123:e752-e762.
4. Bangalore KK, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: Update by an international consortium. *Horm Res Paediatr*. 2019;91(6):357-372.
5. Houk CP, Kunselman AR, Lee PA. Adequacy of a single unstimulated luteinizing hormone level to diagnose central precocious puberty in girls. *Pediatrics*. 2009;123:e1059-e1063.
6. Kaplowitz P, Bloch C, the Section on Endocrinology. Evaluation and referral of children with signs of early puberty. *Pediatrics.* 2016;137:e20153732.
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9. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, 8th version. ©2022 World Professional Association for Transgender Health. Available at http://www.wpath.org.
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FIRMAGON (degarelix)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Firmagon is indicated for the treatment of patients with advanced prostate cancer.

B. Compendial Use
Prostate cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Prostate cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced an unacceptable toxicity.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Firmagon.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Prostate cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Firmagon are covered in addition to prostate cancer in other clinical settings.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for prostate cancer outside the setting of advanced disease can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Firmagon [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; February 2020.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed February 1, 2023.

FOLOTYN (pralatrexate)
pralatrexate

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)

B. Compendial Uses
1. Adult T-cell leukemia/lymphoma (ATLL)
2. Mycosis fungoides/Sezary syndrome (MF/SS)
3. Cutaneous anaplastic large cell lymphoma (ALCL)
4. Extranodal NK/T-cell lymphoma
5. Hepatosplenic T-cell lymphoma
6. Anaplastic large cell lymphoma
7. Peripheral T-cell lymphoma not otherwise specified
8. Angioimmunoblastic T-cell lymphoma
9. Enteropathy associated T-cell lymphoma
10. Monomorphic epitheliotropic intestinal T-cell lymphoma
11. Nodal peripheral T-cell lymphoma with TFH phenotype
12. Follicular T-cell lymphoma
13. Breast implant associated anaplastic large cell lymphoma (ALCL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Peripheral T-cell lymphoma (PTCL)
Authorization of 12 months may be granted for treatment of PTCL (including the following subtypes: anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma) when both of the following criteria are met:
1. The requested medication will be used as a single agent.
2. The requested medication will be used to treat relapsed or refractory disease or for initial palliative therapy.

B. Adult T-cell leukemia/lymphoma (ATLL)
Authorization of 12 months may be granted for treatment of ATLL when both of the following criteria are met:
1. The requested medication is used as a single agent.
2. The requested medication is used as subsequent therapy.

C. Mycosis fungoides/Sezary syndrome (MF/SS)
Authorization of 12 months may be granted for treatment of MF or SS.

D. Cutaneous anaplastic large cell lymphoma

Authorization of 12 months may be granted for treatment of cutaneous anaplastic large cell lymphoma (ALCL) when the requested medication is used as a single agent.

E. Extranodal NK/T-cell lymphoma

Authorization of 12 months may be granted for treatment of extranodal NK/T-cell lymphoma when all of the following criteria are met:

1. The requested medication will be used as a single agent.
2. The member has relapsed or refractory disease.
3. The member has had an inadequate response or contraindication to asparaginase-based therapy (e.g., pegaspargase).

F. Hepatosplenic T-cell lymphoma

Authorization of 12 months may be granted for treatment of hepatosplenic T-cell lymphoma when both of the following criteria are met:

1. The requested medication will be used as a single agent.
2. The member has had two or more previous lines of chemotherapy.

G. Breast implant-associated anaplastic large cell lymphoma (ALCL)

Authorization of 12 months may be granted for treatment of breast implant associated ALCL when both of the following criteria are met:

1. The requested medication will be used as a single agent.
2. The requested medication will be used as subsequent therapy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Folotyn.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: T-Cell Lymphomas
4. NCCN Guideline: Primary Cutaneous Lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Folotyn are covered in addition to primary cutaneous T-cell lymphomas and other T-cell lymphomas, including adult T-cell leukemia/lymphoma (ATLL), extranodal NK/T-cell lymphoma (NKTL), hepatosplenic gamma-delta T-cell lymphoma (HGTL).

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Folotyn to treat primary cutaneous T-cell lymphomas and other T-cell lymphomas, including adult T-cell leukemia/lymphoma (ATLL), extranodal NK/T-cell lymphoma (NKTL), hepatosplenic gamma-delta

T-cell lymphoma (HGTL) can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Folotyn [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; June 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc.. Available at http://www.nccn.org. Accessed November 2023.

FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Fyarro is indicated for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).

B. Compendial Uses
1. PEComa
2. Uterine Sarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Perivascular Epithelioid Cell Tumor (PEComa)
Authorization of 12 months may be granted for the treatment of locally advanced unresectable or metastatic malignant PEComa when used as a single agent.

B. Uterine Sarcoma
Authorization of 12 months may be granted for the treatment of advanced, recurrent, metastatic or inoperable uterine sarcoma (PEComa) when used as a single agent.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
1. No evidence of unacceptable toxicity while on the current regimen AND
2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Fyarro.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. NCCN Guideline: Uterine neoplasms
4. NCCN Guideline: Soft tissue sarcoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Fyarro are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Fyarro to treat uterine sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Fyarro [package insert]. Pacific Palisades, CA: Aadi Bioscience, Inc; December 2021.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 6, 2023.

GAMIFANT (emapalumab-lzsg)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Gamifant is indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

A. The following documentation must be available, upon request, for all submissions:
    1. Medical record documentation (i.e., chart notes or laboratory report) confirming the diagnosis of HLH with the presence of one of the following:
        A) A mutation in one of the following genes: PRF1, UNC13D, STX11 and STXBP2
        OR
        B) Presence of at least 5 clinical signs and symptoms of disease. (See Appendix)

III. CRITERIA FOR INITIAL APPROVAL

A. Primary HLH
Authorization of 6 months may be granted for treatment of primary HLH when all of the following criteria are met:
1. The member has refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.
2. The member's diagnosis of primary HLH was confirmed by either of the following:
    i. Mutation in one of the following genes: PRF1, UNC13D, STX11 and STXBP2
    ii. Presence of at least 5 clinical signs and symptoms of HLH (See Appendix A)
3. Possible causes of secondary or acquired forms of HLH (e.g., autoimmune disease, persistent infection, malignancy, or loss of inhibitory immune mechanisms) have been ruled out.
4. The member has been evaluated for tuberculosis (TB) risk factors and has undergone pretreatment screening for latent TB with the purified protein derivative (PPD) skin test or interferon gamma release assay.
5. If member has a positive test result or is at risk for TB, prophylactic treatment for TB must be initiated before starting therapy.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for primary HLH who have achieved or maintained positive clinical response.

V. APPENDIX

CLINICAL SIGNS AND SYMPTOMS OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

i. Fever
ii. Splenomegaly
iii. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood: hemoglobin less than 9 g/dL [hemoglobin less than 10 g/dL in infants younger than 4 weeks], platelets less than 100,000/microliter, neutrophils less than 1,000/microliter)
iv. Hypertriglyceridemia (fasting triglyceride greater than or equal to 265 mg/dL) or hypofibrinogenemia (less than or equal to 150 mg/dL)
v. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver with no evidence of malignancy
vi. Low or absent natural killer (NK) cell activity
vii. Ferritin greater than or equal to 500 ng/mL
viii. Soluble CD25 (soluble IL-2 receptor alpha) level greater than or equal to 2400 U/mL, or above age-adjusted, laboratory-specific normal levels (defined as 2 standard deviation from the mean)

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Gamifant
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology
3. Any applicable guidelines
    a. Consensus-based guidelines for the recognition, diagnosis, and management of hemophagocytic lymphohistiocytosis in critically ill children and adults
    b. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Gamifant are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCES

1. Gamifant [package insert]. Waltham, MA: Sobi, Inc.; June 2020.
2. Hines MR, von Bahr Greenwood T, Beutel G, et al. Consensus-based guidelines for the recognition, diagnosis, and management of hemophagocytic lymphohistiocytosis in critically ill children and adults. *Crit Care Med*. 2022;50(5):860-872. doi:10.1097/CCM.0000000000005361
3. La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;133(23):2465-2477. doi:10.1182/blood.2018894618

GAZYVA (obinutuzumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Chronic Lymphocytic Leukemia (CLL)
      Gazyva, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated CLL.

   2. Follicular Lymphoma
      1. Gazyva, in combination with bendamustine followed by Gazyva monotherapy, is indicated for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen.
      2. Gazyva, in combination with chemotherapy followed by Gazyva monotherapy in patients achieving at least a partial remission, is indicated for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma.

B. Compendial Uses
   1. Chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/ SLL)
   2. Follicular lymphoma
   3. Marginal zone lymphomas
      a. Extranodal (gastric and non-gastric MALT lymphoma) marginal zone lymphoma
      b. Nodal marginal zone lymphoma
      c. Splenic marginal zone lymphoma
   4. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
   5. Mantle cell lymphoma
   6. Diffuse large B-cell lymphoma
   7. High-grade B-cell lymphomas (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
   8. Burkitt lymphoma
   9. HIV-related B-cell lymphomas
   10. Post-transplant lymphoproliferative disorders
   11. Castleman's disease
   12. Hairy Cell Leukemia

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)
Authorization of 6 months may be granted for the treatment of CLL/SLL as a single agent or in combination with acalabrutinib, venetoclax, chlorambucil, bendamustine, high-dose methylprednisolone (HDMP), or ibrutinib.

B. Follicular Lymphoma (FL)

Authorization of 6 months, up to 30 months total, may be granted for the treatment of follicular lymphoma when any of the following criteria are met:

1. The requested medication will be used in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen, CVP (cyclophosphamide, vincristine and prednisone) regimen, bendamustine, or lenalidomide as first line therapy.
2. The requested medication will be used as a single agent or in combination with lenalidomide, bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CVP (cyclophosphamide, vincristine, and prednisone) for subsequent therapy.
3. The requested medication will be used as maintenance therapy as a single agent.
4. The requested medication will be used as a substitute for rituximab in members experiencing intolerance or rare complications from rituximab such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.

C. Extranodal Marginal Zone Lymphoma and Splenic Marginal Zone Lymphoma

Authorization of 6 months may be granted for the treatment of extranodal marginal zone lymphoma (gastric and non-gastric MALT lymphoma) or splenic marginal zone lymphoma when any of the following criteria are met:

1. The requested medication will be used as subsequent therapy in combination with bendamustine, or lenalidomide.
2. The requested medication will be used as maintenance therapy when the member has been previously treated with the requested medication and bendamustine.
3. The requested medication is used as a substitute for rituximab in members experiencing intolerance or rare complications from rituximab such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.

D. Nodal Marginal Zone Lymphoma

Authorization of 6 months may be granted for the treatment of nodal marginal zone lymphoma when any of the following criteria are met:

1. The requested medication will be used as first-line therapy in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen, CVP (cyclophosphamide, vincristine and prednisone) regimen, or bendamustine.
2. The requested medication will be used as subsequent therapy in combination with bendamustine, or lenalidomide.
3. The requested medication will be used as maintenance therapy when the member has been previously treated with the requested medication and bendamustine.
4. The requested medication is used as a substitute for rituximab in members experiencing intolerance or rare complications from rituximab such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.

E. Hairy Cell Leukemia

Authorization of 6 months may be granted in combination with vemurafenib as initial therapy for treatment of hairy cell leukemia in members who are unable to tolerate purine analogs.

F. Diffuse Large B-Cell Lymphoma when used as pre- treatment with glofitamab (Columvi)

Authorization of 1 month may be granted for treatment of diffuse large B-cell lymphoma when used as pre-treatment for up to 1 dose in cycle 1 of glofitamab therapy.

G. Histologic Transformation of indolent Lymphomas to Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, High-Grade B-Cell Lymphomas(including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified), Burkitt Lymphoma, HIV-Related B-Cell Lymphomas, Post-Transplant Lymphoproliferative Disorders, and Castleman's Disease

Authorization of 6 months may be granted for the treatment of histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, high-

grade B-cell lymphomas (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified), Burkitt lymphoma, HIV-related B-cell lymphomas, post-transplant lymphoproliferative disorders, or Castleman's disease when the requested medication is used as a substitute for rituximab in members experiencing intolerance or rare complications from rituximab such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Follicular Lymphoma (FL)
Authorization of 12 months, up to 30 months total may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat an indication enumerated in Section II.
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen and
    ii. No evidence of disease progression while on the current regimen

B. Diffuse Large B-Cell Lymphoma when used as pre- treatment with glofitamab (Columvi)
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria

C. All other indications
Authorization of 12 months, may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat an indication enumerated in Section II.
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen and
    ii. No evidence of disease progression while on the current regimen

IV. APPENDIX

Re-challenge with the same anti-CD20 monoclonal antibody is not recommended and it is unclear if the use of an alternative anti-CD20 monoclonal antibody poses the same risk of recurrence.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Gazyva and Columvi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Hairy cell leukemia
4. NCCN Guideline: Chronic lymphocytic leukemia/small lymphocytic lymphoma
5. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Gazyva are covered in addition to the following:

1. Chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/ SLL)
2. Follicular lymphoma
3. Marginal zone lymphomas
    a. Extranodal (gastric and non-gastric MALT lymphoma) marginal zone lymphoma
    b. Nodal marginal zone lymphoma
    c. Splenic marginal zone lymphoma
4. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
5. Mantle cell lymphoma
6. Diffuse large B-cell lymphoma
7. High-grade B-cell lymphomas (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
8. Burkitt lymphoma
9. HIV-related B-cell lymphomas
10. Post-transplant lymphoproliferative disorders
11. Castleman's disease
12. Hairy Cell Leukemia

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information. Additionally, the prescribing information for Columvi supports using Gazyva as pretreatment prior to starting treatment with Columvi.

Support for the additional indications listed in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Gazyva [package insert]. South San Francisco, CA: Genentech, Inc.; July 2022.
2. Columvi [package insert]. South San Francisco, CA: Genentech, Inc.; June 2023.
3. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed June 2, 2023.

GIVLAARI (givosiran)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Givlaari is indicated for the treatment of adults with acute hepatic porphyria (AHP).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For initial requests: elevated porphobilinogen (PBG) in the urine confirmed by a PBG quantitative random urine test, or an elevated porphyrin level (plasma or fecal).

III. CRITERIA FOR INITIAL APPROVAL

Acute Hepatic Porphyria
Authorization of 12 months may be granted for treatment of acute hepatic porphyria when all of the following criteria are met:
A. The member is actively symptomatic.
B. The member has an elevated urine porphobilinogen (PBG), or an elevated porphyrin level (plasma or fecal).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., reduction in porphyria attacks that required hospitalizations, urgent healthcare visit, or intravenous hemin administration).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Givlaari.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Givlaari are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information and the ENVISION trial cited in the prescribing information.

VII. REFERENCES

1. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; February 2023.

HEMGENIX (etranacogene dezaparvovec-drlb)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Hemgenix is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with Hemophilia B (congenital Factor IX deficiency) who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Chart notes, lab tests documenting all of the following (where applicable):
A. Severe to moderately severe Factor IX deficiency (≤2% of normal circulating Factor IX)
B. Absence of Factor IX inhibitors (lab test results required)
C. Current use of Factor IX prophylaxis therapy
D. History of life-threatening hemorrhage(s) or repeated, serious spontaneous bleeding episodes.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a hematologist.

IV. CRITERIA FOR INITIAL APPROVAL

Hemophilia B
Authorization of 1 month for one dose total may be granted for the treatment of severe or moderately severe hemophilia B when all of the following criteria are met:
A. Member is 18 years of age or older
B. Member meets either of the following:
    1. Member has a negative Factor IX inhibitor test result within the past 30 days
    2. If member has a positive Factor IX inhibitor test result within the past 30 days, there must be a negative test result within 2 weeks of the initial positive result
C. Member has severe or moderately severe Factor IX deficiency (≤2% of normal circulating Factor IX) and meets any of the following:
    1. Member is currently using Factor IX prophylactic therapy
    2. Member has a current or history of a life-threatening hemorrhage
    3. Member has a history of repeated, serious spontaneous bleeding episodes
D. Member has not previously received gene therapy treatment

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Hemgenix.
2. The available compendium

a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Hemgenix are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Hemgenix [package insert]. King of Prussia, PA: CSL Behring LLC; November 2022.

HEMLIBRA (emicizumab-kxwh)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Hemlibra is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For continuation requests: Chart notes documenting benefit from therapy (e.g., reduced frequency or severity of bleeds).

III. CRITERIA FOR INITIAL APPROVAL

Hemophilia A (congenital factor VIII deficiency)
Authorization of 12 months may be granted for treatment of hemophilia A (congenital factor VIII deficiency) when all of the following criteria is met:
A. Member must be using the requested medication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
B. Member meets one of the following criteria:
    1. Member has mild disease (See Appendix A) and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (See Appendix B).
    2. Member has moderate or severe disease (See Appendix A).
C. Prophylactic use of factor VIII products (e.g., Advate, Adynovate, Eloctate) will be discontinued after the first week of starting therapy with the requested medication.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds)
D. The member is not using the requested medication in combination with factor VIII products (e.g., Advate, Adynovate, Eloctate, etc.) for prophylactic use.

V. DOSAGE AND ADMINISTRATION[1]

For initial and continuation requests, dosing does not exceed the following:

A. Induction: 3 mg/kg subcutaneously once weekly for the first 4 weeks.
B. Maintenance: 1.5 mg/kg once weekly, or 3 mg/kg once every 2 weeks, or 6 mg/kg once every 4 weeks.

VI. APPENDICES

Appendix A: Classification of Hemophilia by Clotting Factor Level (% Activity) and Bleeding Episodes

Severity	Clotting Factor Level % activity*	Bleeding Episodes
Severe	<1%	Spontaneous bleeding episodes, predominantly into joints and muscles Severe bleeding with trauma, injury or surgery
Moderate	1% to 5%	Occasional spontaneous bleeding episodes Severe bleeding with trauma, injury or surgery
Mild	6% to 40%	Severe bleeding with serious injury, trauma or surgery

*Factor assay levels are required to determine the diagnosis and are of value in monitoring treatment response.

Appendix B: Clinical Reasons For Not Utilizing Desmopressin in Patients with Hemophilia A

a. Age < 2 years
b. Pregnancy
c. Fluid/electrolyte imbalance
d. High risk for cardiovascular or cerebrovascular disease (especially the elderly)
e. Predisposition to thrombus formation
f. Trauma requiring surgery
g. Life-threatening bleed
h. Contraindication or intolerance to desmopressin
i. Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Hemlibra.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, 3rd edition
4. National Hemophilia Foundation (NHF) Medical and Scientific Advisor Council (MASAC) Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Hemlibra are covered.

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Hemlibra to treat mild hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Mild disease is defined as having a clotting factor level of 6 to 40% of normal. The patient generally experiences severe bleeding with major trauma or surgery. It is rare these patients will bleed spontaneously. Desmopressin may be the treatment of choice for patients with mild hemophilia A when factor VIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of

using clotting factor concentrates. Desmopressin is not appropriate in all situations. Patients under 2 years of age, pregnant patients, patients with electrolytes or fluid imbalance, patients at high risk for cerebrovascular disease, predisposition to thrombus formation, patients who experienced trauma severe enough to require surgery, and patients experiencing a life-threatening bleed are not ideal candidates for desmopressin therapy.

Support for using Hemlibra to treat moderate to severe hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Patients with moderate to severe hemophilia A should be started on prophylaxis with factor VIII or a non-factor therapy like Hemlibra to prevent a recurring life-threatening bleed. Desmopressin is not appropriate in these patients.

IX. REFERENCES

1. Hemlibra [package insert]. South San Francisco, CA: Genentech, Inc.; March 2023.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
3. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 7, 2023.
4. National Hemophilia Foundation. Hemophilia A (Factor VIII Deficiency). Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=180&contentid=45&rptname=bleeding. Accessed December 7, 2023.
5. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed December 7, 2023.
6. Leissinger C, Carcao M, Gill JC, et al. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. *Haemophilia*. 2014;20:158-167.

HERCEPTIN (trastuzumab)
KANJINTI (trastuzumab-anns)
OGIVRI (trastuzumab-dkst)
TRAZIMERA (trastuzumab-qyyp)
HERZUMA (trastuzumab-pkrb)
ONTRUZANT (trastuzumab-dttb)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Adjuvant breast cancer
   Adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-overexpressing node positive or node negative (estrogen receptor (ER)/progesterone receptor (PR) negative or with one high risk feature) breast cancer
   a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
   b. As part of a treatment regimen with docetaxel and carboplatin
   c. As a single agent following multi-modality anthracycline based therapy
2. Metastatic breast cancer
   a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
   b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease
3. Metastatic gastric cancer
   In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease

B. Compendial Uses
1. HER2-positive breast cancer:
   a. Neoadjuvant therapy
   b. Treatment of recurrent, advanced unresectable, or stage IV (M1) disease
   c. Treatment for no response to preoperative systemic therapy
2. HER2-negative breast cancer treatment of stage IV (M1) disease
3. Intra-cerebrospinal fluid (CSF) treatment of leptomeningeal metastases (malignant meningitis) from HER2-positive breast cancer
4. HER2-positive esophageal and esophagogastric junction cancer
5. HER2- positive uterine serous carcinoma and carcinosarcoma
6. HER2-positive salivary gland tumors
7. HER2-amplified and RAS and BRAF wild-type colorectal cancer
8. HER2-positive biliary tract cancers
9. HER2-positive non-small cell lung cancer
10. Prostate cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Human epidermal growth factor receptor 2 (HER2) status, where applicable
B. RAS mutation status, where applicable
C. BRAF mutation status, where applicable

III. CRITERIA FOR INITIAL APPROVAL

A. Breast Cancer
1. Authorization of 12 months may be granted for neoadjuvant treatment of HER2-positive breast cancer as part of a complete treatment regimen.
2. Authorization of 12 months may be granted for adjuvant treatment of HER2-positive breast cancer.
3. Authorization of 12 months may be granted for treatment of HER2-positive breast cancer with no response to preoperative systemic therapy, recurrent, advanced, unresectable, or metastatic (including brain metastases) disease.
4. Authorization of 12 months may be granted for intra-CSF treatment of leptomeningeal metastases (malignant meningitis) from HER2-positive breast cancer.
5. Authorization of 12 months may be granted for treatment of stage IV HER2-negative breast cancer when used in combination with neratinib and fulvestrant.

B. Esophageal, Gastric, or Esophagogastric Junction Cancer
Authorization of 12 months may be granted for treatment or palliative therapy of HER2-positive esophageal, gastric, or esophagogastric junction cancer in combination with chemotherapy.

C. Uterine Serous Carcinoma or Carcinosarcoma
Authorization of 12 months may be granted for treatment of HER2-positive stage III-IV, metastatic or recurrent uterine serous carcinoma or carcinosarcoma in combination with carboplatin and paclitaxel.

D. Salivary Gland Tumors
Authorization of 12 months may be granted for treatment of recurrent, unresectable, or metastatic HER2-positive salivary gland tumors when used as a single agent or in combination with docetaxel or pertuzumab.

E. Colorectal Cancer
Authorization of 12 months may be granted for treatment of unresectable, inoperable, advanced, or metastatic colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, when all of the following criteria are met:
1. Member has HER2-positive/amplified disease
2. The disease is negative (wild-type) for RAS (KRAS and NRAS) and BRAF mutations
3. The requested medication will be used in combination with tucatinib, pertuzumab, or lapatinib
4. Member has received prior therapy for the disease or is not appropriate for intensive therapy

F. Biliary Tract Cancers
Authorization of 12 months may be granted for subsequent treatment of unresectable, resected gross residual, or metastatic HER2-positive biliary tract cancers (including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer) when used in combination with pertuzumab.

G. Non-Small Cell Lung Cancer
Authorization of 12 months may be granted for treatment of HER2-positive non-small cell lung cancer.

H. Prostate Cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for all members (including new members) when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat a diagnosis or condition enumerated in Section III.
C. For members requesting reauthorization for adjuvant or neoadjuvant treatment of breast cancer, the maximum treatment duration is 12 months.
D. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Herceptin, Kanjinti, Ogivri, Trazimera, Herzuma, and Ontruzant.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Breast cancer
4. NCCN Guideline: Gastric cancer
5. NCCN Guideline: Esophageal and esophagogastric junction cancers
6. NCCN Guideline: Central nervous system cancers
7. NCCN Guideline: Biliary tract cancers
8. NCCN Guideline: Colon cancer
9. NCCN Guideline: Uterine neoplasms
10. NCCN Guideline: Rectal cancer
11. NCCN Guideline: Head and neck cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Herceptin, Kanjinti, Ogivri, Trazimera, Herzuma and Ontruzant are covered in addition to the following:

1. HER2-positive breast cancer:
    a. Neoadjuvant therapy
    b. Treatment of recurrent or advanced unresectable disease
    c. Treatment for no response to preoperative systemic therapy
2. HER2-negative breast cancer
3. Intra-cerebrospinal fluid (CSF) treatment of leptomeningeal metastases (malignant meningitis) from HER2-positive breast cancer
4. HER2-positive esophageal and esophagogastric junction cancer
5. HER2- positive uterine serous carcinoma and carcinosarcoma
6. HER2-positive salivary gland tumors
7. HER2-amplified and RAS and BRAF wild-type colorectal cancer
8. HER2-positive biliary tract cancers
9. HER2-positive non-small cell lung cancer
10. Prostate cancer

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for all indications other than non-small cell lung cancer and prostate cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-

label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for non-small cell lung cancer and prostate cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Herceptin [package insert]. South San Francisco, CA: Genentech, Inc.; February 2021.
2. Kanjinti [package insert]. Thousand Oaks, CA: Amgen, Inc.; October 2022.
3. Ogivri [package insert]. Zurich, Switzerland: Mylan GmbH; July 2023.
4. Trazimera [package insert]. Cork, Ireland: Pfizer Ireland Pharmaceuticals; November 2020.
5. Herzuma [package insert]. Incheon, Republic of Korea: Celltrion, Inc. May 2019.
6. Ontruzant [package insert]. Incheon, Republic of Korea: Samsung Bioepis Co.; June 2021.
7. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed December 5, 2023.
8. Micromedex Solutions [electronic version]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed December 5, 2023.
9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Anal Carcinoma. Version 3.2023. Accessed December 5, 2023. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers. Version 4.2024. Accessed December 21, 2023. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

HERCEPTIN HYLECTA (trastuzumab and hyaluronidase-oysk)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Herceptin Hylecta is indicated for adjuvant treatment of adults with HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:
      i. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
      ii. As part of a treatment regimen with docetaxel and carboplatin
      iii. As a single agent following multi-modality anthracycline based therapy

   2. Herceptin Hylecta is indicated in adults:
      i. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
      ii. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

B. Compendial Uses
   HER2-positive breast cancer: may be substituted for intravenous trastuzumab and used as a single agent or in combination with other systemic therapies

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Human epidermal growth factor receptor 2 (HER2) status.

III. CRITERIA FOR INITIAL APPROVAL

Breast Cancer

A. Authorization of up to 12 months may be granted for treatment of adjuvant treatment of HER2-positive breast cancer.
B. Authorization of 12 months may be granted for treatment of HER2-positive breast cancer with no response to preoperative systemic therapy, recurrent, unresectable, advanced, or metastatic (including brain metastases) disease.
C. Authorization of up to 12 months may be granted for neoadjuvant treatment of HER2-positive breast cancer as part of a complete treatment regimen.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Breast Cancer in the Adjuvant and Neoadjuvant Setting

Authorization of 12 months (up to 12 months total) may be granted for adjuvant or neoadjuvant treatment of breast cancer when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication
2. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

B. Breast Cancer with No Response to Preoperative Therapy or in the Recurrent, Unresectable, Advanced, or Metastatic Setting

Authorization of 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication
2. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Herceptin Hylecta.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Breast cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Herceptin Hylecta are covered in addition to using Herceptin Hylecta as a substitute for intravenous trastuzumab for HER2-positive breast cancer.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Herceptin Hylecta as a substitute for intravenous trastuzumab to treat HER2-positive breast cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Herceptin Hylecta may be used as a single agent or in combination with other systemic therapies. Do not substitute for or with ado-trastuzumab emtansine (Kadcyla) or fam-trastuzumab deruxtecan-nxki (Enhertu).

VII. REFERENCES

1. Herceptin Hylecta [package insert]. South San Francisco, CA: Genentech, Inc.; February 2019.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 28, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed November 28, 2023.

DUROLANE (hyaluronic acid)
EUFLEXXA (1% sodium hyaluronate)
GEL-ONE (cross-linked hyaluronate)
GELSYN-3 (sodium hyaluronate 0.84%)
GENVISC 850 (sodium hyaluronate)
HYALGAN (sodium hyaluronate)
HYMOVIS (high molecular weight viscoelastic hyaluronan)
MONOVISC (high molecular weight hyaluronan)
ORTHOVISC (high molecular weight hyaluronan)
SUPARTZ FX (sodium hyaluronate)
SYNOJOYNT (1% sodium hyaluronate)
SYNVISC (hylan G-F 20)
SYNVISC ONE (hylan G-F 20)
TRILURON (sodium hyaluronate)
TRIVISC (sodium hyaluronate)
VISCO-3 (sodium hyaluronate)
1% sodium hyaluronate

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

B. Compendial Uses
1. Treatment of pain of arthropathy of the shoulder
2. Treatment of subacromial impingement
3. Treatment of temporomandibular joint disorder

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Osteoarthritis of the Knee or Shoulder
Authorization of 12 months may be granted for treatment of osteoarthritis in the knee or shoulder.

B. Subacromial impingement
Authorization of 3 months may be granted for treatment of subacromial impingement.

C. Temporomandibular joint disorder
Authorization of 3 months may be granted for treatment of temporomandibular joint disorder.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Osteoarthritis of the Knee or Shoulder

Authorization of 12 months for osteoarthritis of the knee or shoulder may be granted when ALL of the following criteria are met:

1. The member has previously received therapy in the same joint with a hyaluronate product.
2. The member meets either of the following:
    i. The member will receive the first injection of the retreatment course after at least 6 months from the last injection of the previous completed course and the medication has been effective for treating the diagnosis or condition.
    ii. A different hyaluronate product is being requested due to an adverse event with the previous course.

B. All Other Indications

Authorization of 3 months may be granted for all other indications when ALL of the following criteria are met:

1. The hyaluronate product is being used to treat an indication enumerated in Section II.
2. The medication has been effective for treating the diagnosis or condition.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for the above referenced hyaluronate products.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2019 American College of Rheumatology/Arthritis Foundation Guidelines for the management of osteoarthritis of the hand, hip, and knee.
4. Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the above referenced hyaluronate products are covered in addition to the following:

A. Osteoarthritis of the shoulder
B. Subacromial impingement
C. Temporomandibular joint disorder

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for knee osteoarthritis can be found in the OARSI guidelines from 2019. Intra-articular corticosteroids and hyaluronan injections are conditionally recommended in individuals with knee osteoarthritis in all groups. Intra-articular hyaluronic acid may have beneficial effects on pain at and beyond 12 weeks of treatment. Hyaluronic acid injections may have a more favorable long-term safety profile compared to repeated intra-articular corticosteroid injections.

Conversely, the American College of Rheumatology and Arthritis Foundation Guideline states that intra-articular hyaluronic acid injections are conditionally recommended against in patients with knee osteoarthritis. In prior systematic reviews, apparent benefits of hyaluronic acid injections in OA have been reported. These reviews have not, however, taken into account the risk of bias of the individual primary studies. Our review showed that benefit was restricted to the studies with higher risk of bias: when limited to trials with low risk of

bias, meta-analysis has shown that the effect size of hyaluronic acid injections compared to saline injections approaches zero. The finding that best evidence fails to establish a benefit, and that harm may be associated with these injections, motivated the recommendation against use of this treatment.

Many providers want the option of using hyaluronic acid injections when glucocorticoid injections or other interventions fail to adequately control local joint symptoms. In clinical practice, the choice to use hyaluronic acid injections in the knee OA patient who has had an inadequate response to nonpharmacologic therapies, topical and oral NSAIDs, and intraarticular steroids may be viewed more favorably than offering no intervention, particularly given the impact of the contextual effects of intraarticular hyaluronic acid injections. The conditional recommendation against is consistent with the use of hyaluronic acid injections, in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit.

Support for shoulder osteoarthritis can be found in a study where patients were administered weekly injection of 25 mg sodium hyaluronate (high molecular weight) into the glenoid cavity or subacromial bursa. The injections improved pain at rest, pain on motion, and pain on pressure in approximately 75% of 62 patients with periarthritis of the shoulder. A series of 5 injections was planned, and further injections were discontinued if pain was resolved. If not, weekly or biweekly injections continued. The mean treatment was 6 ampules injected over 8 weeks, but ranged from 1 to 27 injections given over 2 to 40 weeks. Final global improvement ratings showed 11% markedly improved, 40% moderately improved, 31% slightly improved, and 18% unchanged. None worsened. Among activities of daily living improved more than 60% were hair grooming, tying a sash behind the back, removing upper garments, or being able to touch the opposite shoulder. Range of motion improved in each measure, with the greatest change noted in the angle of abduction.

Support for subacromial impingement can be found in a randomized, single-blind, open-comparator clinical study (n=80). Hyaluronate 20 mg injected into the subacromial space once weekly for 3 weeks was associated with greater self-rated pain relief of subacromial impingement syndrome of the shoulder compared with a single dexamethasone injection, although improvement in functional scores and use of rescue medication were similar. Participants older than 40 years of age who had subacromial impingement syndrome without a rotator cuff tear and who had pain for 3 months or longer without improvement despite conservative treatment with physiotherapy and NSAIDs were randomized to hyaluronate sodium 20 mg subacromial injection once weekly for 3 weeks (n=38; mean age, 55.9 years) or a single subacromial injection of dexamethasone disodium phosphate 5 mg with 4 mL lidocaine 2% (n=42; mean age, 54.1 years). In both treatment arms, the 100-point visual analogue scale (VAS) score decreased significantly from baseline to week 12, from 58.6 to 24.6 in the hyaluronate group (p less than 0.0001) and from 57.2 to 36.9 in the dexamethasone group (p less than 0.0001). The hyaluronate group demonstrated a significantly greater decrease in the VAS score at 12 weeks compared with the dexamethasone group (p=0.018). Functional score from baseline to week 12, assessed by the American Shoulder and Elbow Surgeons (ASES) standardized shoulder assessment form, improved from 18.2 to 22.8 in the hyaluronate group (p=0.0023) and from 17.5 to 21.9 in the dexamethasone group (p=0.0002), although no significant difference was observed between the treatment groups at week 12. The use of acetaminophen for rescue pain relief was similar between the hyaluronate and dexamethasone groups (26 of 38 and 29 of 42, respectively). Adverse events were generally mild, with nasopharyngitis (hyaluronate, 15.38%; dexamethasone, 13.46%) and muscle pain (hyaluronate, 9.62%; dexamethasone, 3.85%) reported most frequently.

Support for temporomandibular joint disorder can be found in a study where patients were injected with sodium hyaluronate into the articular cavities with internal derangement of temporomandibular joints (TMJs). The procedure decreased friction so that, surgically, the articular disc could be retracted and, clinically, degree of mouth opening increased in some patients. After 63 patients were randomized into either a test group of 43 patients (45 TMJs, 29 with disc displacement with reduction and 16 without reduction) or a control group of 20 patients (24 TMJs, 17 with disc displacement with reduction and 7 without reduction), injections were made into the articular cavity. Test-group patients received 0.3 to 1 mL sodium hyaluronate 1% up to 3 times, either into the upper cavity only or into both upper and lower cavities, while control-group patients received 1 mL of lidocaine 2%. At follow-up visits relief of joint pain was evaluated as very good, good, or of no effect. Results were very good for 17 TMJs in the test group and 4 in the control group; good for 19 in the test group and 8 in the control group; and of no effect for 9 in the test group and 12 controls (chi(2)=6.6535, p less than 0.01). The difference between disc displacement with reduction and without reduction was not significant.

VI. REFERENCES

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15. Trivisc [package insert]. Doylestown, PA: OrthogenRx, Inc.; December 2017.
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FIRAZYR (icatibant)
Sajazir (icatibant)
icatibant

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.

B. Compendial Use
Treatment of angiotensin-converting enzyme (ACE) inhibitor-induced angioedema

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Hereditary angioedema (HAE):
A. For initial authorization:
   1. C1 inhibitor functional and antigenic protein levels
   2. F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
   3. Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
B. For continuation of therapy, chart notes demonstrating a reduction in severity and/or duration of attacks

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

IV. CRITERIA FOR INITIAL APPROVAL

A. Hereditary angioedema (HAE)
Authorization of 6 months may be granted for treatment of acute HAE attacks when either of the following criteria is met at the time of diagnosis:
1. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
   a. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
   b. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
2. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:

a. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
b. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

B. ACE inhibitor-induced angioedema
Authorization of 3 days may be granted for acute management of ACE inhibitor-induced angioedema.

V. CONTINUATION OF THERAPY

A. Hereditary angioedema
All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment of acute HAE attacks when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy. Benefit is defined as a reduction in severity and/or duration of acute attacks.

B. ACE inhibitor-induced angioedema
All members (including new members) requesting reauthorization for continuation of therapy must meet all initial authorization criteria.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Firazyr, Sajazir and generic icatibant.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.
4. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
5. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
6. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.
7. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
8. International consensus on hereditary and acquired angioedema.
9. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.
10. Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Firazyr, Sajazir, and generic icatibant are covered in addition to ACE inhibitor-induced angioedema.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.
When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

Support for using Firazyr, Sajazir, and generic icatibant to treat ACE inhibitor-induced angioedema can be found in two published studies. Sinert and colleagues found that there was no significant difference in time to meeting discharge criteria between icatibant 30 mg injected subcutaneously and placebo in adults who presented within 12 hours of ACE inhibitor-induced angioedema of the head and/or neck of at least moderate severity (N=121). In both groups, the median time to meeting discharge criteria (defined as time from study drug administration to earliest absence of difficulty breathing or swallowing and mild or absent voice change and tongue swelling) was 4 hours. Median time to symptom resolution was 2 hours with icatibant and 1.6 hours with placebo, which was a nonsignificant difference. The median time to study drug administration after symptom onset was 7.8 hours, and more than 90% of patients also received corticosteroids, antihistamines, or epinephrine prior to the study drug. The most common ACE inhibitor taken by the patients was lisinopril (69.4%). Attack severity was moderate in 71.9% and severe or very severe in 28.1%. Black or African American patients made up 69.4% of the population. The most common treatment-related adverse events with icatibant were increased serum uric acid (n=2), increased neutrophil percentage (n=2), and dysphonia (n=2), and angioedema (n=3). Additionally, Bas and colleagues conducted a randomized trial (N=27) of adults who had ACE inhibitor-induced angioedema. All patients who received either icatibant 30 mg subcutaneously or the off-label standard therapy (prednisolone 500 mg IV plus clemastine 2 mg) achieved complete resolution of edema. However, the median time to complete resolution was significantly shorter with icatibant (8 vs 27.1 hours).

VIII. REFERENCES

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2. icatibant [package insert]. Berkeley Heights, NJ: Hikma Pharmaceuticals; June 2022.
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iDose TR (travoprost intracameral implant)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
iDose® TR is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSION

Coverage will not be provided for members with any of the following exclusions:
A. Active or suspected ocular or periocular infections.
B. Corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy, corneal guttatae).
C. Prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]).
D. Hypersensitivity to travoprost.

III. CRITERIA FOR INITIAL APPROVAL

A. **Open-Angle Glaucoma**
Authorization of 12 months (maximum of 1 implant per affected eye) may be granted for treatment of open-angle glaucoma when the following criteria is met:
1. iDose TR will not be administered to an eye that has received a prior administration of iDose TR.

B. **Ocular Hypertension**
Authorization of 12 months (maximum of 1 implant per affected eye) may be granted for treatment of ocular hypertension when the following criteria is met:
1. iDose TR will not be administered to an eye that has received a prior administration of iDose TR.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for iDose TR.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for iDose TR are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. iDose TR [package insert]. San Clemente, CA: Glaukos Corporation; December 2023.

ILARIS (canakinumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Cryopyrin-associated periodic syndromes (CAPS) in adults and children 4 years of age and older including: Familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS)
2. Tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients
3. Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD) in adult and pediatric patients
4. Familial Mediterranean Fever (FMF) in adult and pediatric patients
5. Active Still's disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older
6. Symptomatic treatment of adult patients with gout flares in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Cryopyrin-associated periodic syndromes (CAPS)
Authorization of 12 months may be granted for treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).

B. Tumor necrosis factor receptor associated periodic syndrome (TRAPS)
Authorization of 12 months may be granted for treatment of tumor necrosis factor receptor associated periodic syndrome (TRAPS).

C. Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD)
Authorization of 12 months may be granted for treatment of hyperimmunoglobulin D syndrome (HIDS) or mevalonate kinase deficiency (MKD).

D. Familial Mediterranean Fever (FMF)
Authorization of 12 months may be granted for treatment of familial Mediterranean Fever (FMF).

E. Systemic juvenile idiopathic arthritis
Authorization of 12 months may be granted for treatment of active systemic juvenile idiopathic arthritis.

F. Active adult-onset Still's disease
Authorization of 12 months may be granted for treatment of active adult-onset Still's disease.

G. Gout flares
Authorization of 12 months may be granted for the treatment of gout flares when the member has had an inadequate response, intolerance, or contraindication to non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Ilaris.
B. Ilaris is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy as evidenced by low disease activity or improvement in signs and symptoms of the condition.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Ilaris.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ilaris are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Ilaris [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2023.

ILUMYA (tildrakizumab-asmn)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Ilumya is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

III. CRITERIA FOR INITIAL APPROVAL

Plaque psoriasis
Authorization of 12 months may be granted for the treatment of moderate to severe plaque psoriasis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Ilumya.
B. Ilumya is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Ilumya.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4: Guidelines of care for the management and treatment of psoriasis with traditional systemic agents.
4. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions.
5. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics.

6. Joint AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologic therapies.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ilumya are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

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5. Menter A, Gelfand JM, Connor C, et al. Joint AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol.* 2020;82(6):1445-1486.

ILUVIEN (fluocinolone acetonide intravitreal implant)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Iluvien is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Diabetic Macular Edema (DME)
Authorization of 12 months may be granted for treatment of diabetic macular edema when all of the following criteria are met:
1. The member has previous been treated with a course of corticosteroids
2. The member did not have a clinically significant rise in intraocular pressure from corticosteroid treatment
3. The member does not have an active or suspected ocular or periocular infection
4. The member does not have glaucoma with a cup-to-disc ratio of greater than 0.8

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Iluvien.
B. The member is receiving benefit from therapy (e.g. stabilization of visual acuity or improvement in best corrected visual acuity (BCVA) score when compared to baseline)
C. The member has no evidence of unacceptable toxicity while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Iluvien
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Iluvien are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Iluvien [package insert]. Alpharetta, GA; Alimera Sciences, Inc; November 2016. Accessed November 2023.

IMFINZI (durvalumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Imfinzi is indicated for the treatment of adult patients with unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
   2. Imfinzi, in combination with etoposide and either carboplatin or cisplatin, is indicated as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
   3. Imfinzi, in combination with gemcitabine and cisplatin, is indicated for the treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC).
   4. Imfinzi, in combination with tremelimumab-actl, is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).
   5. Imfinzi, in combination with tremelimumab-actl and platinum-based chemotherapy, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

B. Compendial Uses
   1. Cervical Cancer
   2. Non-Small Cell Lung Cancer
   3. Small Cell Lung Cancer
   4. Ampullary Adenocarcinoma
   5. Pleural Mesothelioma
   6. Hepatocellular Carcinoma
   7. Esophageal and Esophagogastric Junction Cancer
   8. Gastric Cancer
   9. Biliary Tract Cancer
      a. Intrahepatic Cholangiocarcinoma
      b. Extrahepatic Cholangiocarcinoma
      c. Gallbladder Cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions where applicable:
A. Documentation of the absence of EGFR and ALK genomic aberration (unless testing is not feasible due to insufficient tissue).
B. Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor status, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Non-small cell lung cancer (NSCLC)
Authorization of 12 months may be granted for treatment of NSCLC when either of the following criteria are met:

1. The member has unresectable stage II or III NSCLC that has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
2. The member has recurrent, advanced or metastatic NSCLC and meets all of the following criteria:
   a. The requested medication will be used in combination with tremelimumab-actl (Imjudo) and platinum-based chemotherapy
   b. The tumor is negative for EGFR exon 19 deletion and L858R mutations and ALK rearrangements.

B. Extensive-stage small cell lung cancer (ES-SCLC)
Authorization of 12 months may be granted for first-line treatment of extensive-stage small cell lung cancer in combination with etoposide and either carboplatin or cisplatin followed by single agent maintenance.

C. Cervical Cancer
Authorization of 12 months may be granted for treatment of persistent, recurrent or metastatic small cell neuroendocrine carcinoma of the cervix (NECC) when used in combination with etoposide and either cisplatin or carboplatin.

D. Ampullary Adenocarcinoma
Authorization of 12 months may be granted for first-line treatment of unresectable or metastatic ampullary adenocarcinoma when both of the following criteria are met:
1. The disease is pancreatobiliary or mixed type
2. The requested medication will be used in combination with cisplatin and gemcitabine

E. Pleural Mesothelioma
Authorization of 12 months may be granted for first-line treatment of unresectable pleural mesothelioma when used in combination with pemetrexed and either cisplatin or carboplatin.

F. Hepatocellular Carcinoma
Authorization of 12 months may be granted for treatment of hepatocellular carcinoma when either of the following criteria are met:
1. The requested medication will be used for first-line single agent treatment of unresectable/inoperable, metastatic, or extensive liver tumor burden hepatocellular carcinoma.
2. The requested medication will be used in combination with tremelimumab-actl (Imjudo) for first-line treatment of unresectable/inoperable, metastatic, or extensive liver tumor burden hepatocellular carcinoma.

G. Esophageal, Esophagogastric Junction and Gastric Cancer
Authorization of 3 months for a total of 3 doses may be granted for treatment of esophageal, esophagogastric junction or gastric cancer when all of the following criteria are met:
1. The requested medication will be used in combination with tremelimumab (Imjudo) for neoadjuvant treatment
2. The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR)
3. The member is medically fit for surgery

H. Biliary Tract Cancer
Authorization of 12 months may be granted for treatment of biliary tract cancer when the requested medication will be used in combination with cisplatin and gemcitabine to treat locally advanced, unresectable or resected gross residual (R2) disease, or metastatic biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer) or for disease recurrence after surgery and adjuvant therapy.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

For NSCLC

Authorization for 12 months (or up to a total of 12 months for unresectable stage II or III non-small cell lung cancer) may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen
   ii. No evidence of disease progression while on the current regimen

For Esophageal, Esophagogastric Junction and Gastric Cancer
Authorization for 3 months for a total of 3 doses may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen
   ii. No evidence of disease progression while on the current regimen

For All Other Indications
Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen
   ii. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Imfinzi.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Small cell lung cancer
4. NCCN Guideline: Non-small cell lung cancer
5. NCCN Guideline: Hepatocellular carcinoma
6. NCCN Guideline: Biliary tract cancers
7. NCCN Guideline: Cervical cancer
8. NCCN Guideline: Ampullary adenocarcinoma
9. NCCN Guideline: Gastric cancer
10. NCCN Guideline: Esophageal and esophagogastric junction cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Imfinzi are covered in addition to the following:
   A. Unresectable stage II non-small cell lung cancer
   B. Intrahepatic cholangiocarcinoma
   C. Extrahepatic cholangiocarcinoma
   D. Gallbladder cancer
   E. Hepatocellular carcinoma
   F. Cervical cancer
   G. Ampullary adenocarcinoma
   H. Gastric cancer
   I. Esophageal and esophagogastric junction cancers
   J. Pleural mesothelioma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Imfinzi to treat unresectable stage II NSCLC can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Imfinzi to treat hepatobiliary cancers can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Imfinzi to treat hepatocellular carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Imfinzi to treat cervical cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Imfinzi to treat ampullary adenocarcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Imfinzi to treat gastric cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Imfinzi to treat esophageal and esophagogastric junction cancers can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Imfinzi to treat pleural mesothelioma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Imfinzi [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; June 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 1, 2023.
3. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com Accessed December 1, 2023.
4. Pietrantonio, Filippo, Raimondi Alessandra, Lonardi Sara, et al. Infinity: A multicenter, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). *Journal of Clinical Oncology*. 2023; 4: 358.

IMJUDO (tremelimumab-actl)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Imjudo is indicated in combination with durvalumab for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).
   2. Imjudo is indicated in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

B. Compendial Uses
   1. Recurrent and advanced NSCLC
   2. Esophageal and esophagogastric junction cancer
   3. Gastric cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions where applicable:

A. Documentation of the absence of EGFR exon 19 deletion and L858R mutations and ALK rearrangements (unless testing is not feasible due to insufficient tissue).
B. Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor status, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Hepatocellular Carcinoma

Authorization of 1 month for a one-time single dose may be granted for treatment of hepatocellular carcinoma when all of the following criteria are met:

1. The requested medication will be used in combination with durvalumab (Imfinzi)
2. The disease is unresectable/inoperable, metastatic or has extensive liver tumor burden

B. NSCLC

Authorization of 6 months for a total of 5 doses may be granted for treatment of recurrent, advanced or metastatic non-small cell lung cancer when all of the following criteria are met:

1. The requested medication will be used in combination with durvalumab (Imfinzi) and platinum-based chemotherapy
2. The tumor is negative for EGFR exon 19 deletion and L858R mutations and ALK rearrangements.

C. Esophageal, Esophagogastric Junction and Gastric Cancer

Authorization of 1 month for a one-time single dose may be granted for treatment of esophageal, esophagogastric junction or gastric cancer when all of the following criteria are met:

1. The requested medication will be used in combination with durvalumab (Imfinzi) for neoadjuvant treatment

2. The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR)
3. The member is medically fit for surgery

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Imjudo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Non-small cell lung cancer
4. NCCN Guideline: Hepatocellular carcinoma
5. NCCN Guideline: Gastric cancer
6. NCCN Guideline: Esophageal and esophagogastric junction cancers

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Imjudo to treat gastric cancer and esophageal and esophagogastric junction cancers can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Imjudo [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; June 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed December 1, 2023.
3. Pietrantonio, Filippo, Raimondi Alessandra, Lonardi Sara, et al. Infinity: A multicenter, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). *Journal of Clinical Oncology*. 2023; 4: 358.

IMLYGIC (talimogene laherparepvec)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

B. Compendial Uses
1. Limited resectable or unresectable stage III melanoma with clinical satellite/in-transit metastases or with nodal lesions
2. Oligometastatic melanoma
3. Widely disseminated distant metastatic melanoma
4. Limited resectable or unresectable local satellite/in-transit recurrence of melanoma
5. In combination with ipilimumab for metastatic or unresectable disease as subsequent therapy for disease progression or after maximum clinical benefit from BRAF targeted therapy
6. Merkel cell carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Melanoma
Authorization of 12 months may be granted for treatment of metastatic, unresectable, limited resectable, or incompletely resectable cutaneous, subcutaneous, and nodal lesions in melanoma.

B. Merkel cell carcinoma
Authorization of 12 months may be granted for treatment as a single agent of metastatic Merkel cell carcinoma when one of the following criteria is met:
1. The member has contraindication to anti-PD-L1 or anti-PD-1 therapy.
2. The member has disease progression while on anti-PD-L1 or anti-PD-1 therapy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen, and
   ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Imlygic.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Cutaneous melanoma
4. NCCN Guideline: Merkel cell carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Imlygic are covered in addition to the following:

1. Limited resectable or unresectable stage III melanoma with clinical satellite/in-transit metastases or with nodal lesions
2. Oligometastatic melanoma
3. Widely disseminated distant metastatic melanoma
4. Limited resectable or unresectable local satellite/in-transit recurrence of melanoma
5. In combination with ipilimumab for metastatic or unresectable disease as subsequent therapy for disease progression or after maximum clinical benefit from BRAF targeted therapy
6. Merkel cell carcinoma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Imlygic to treat the clinical scenarios listed in section IV can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Imlygic [package insert]. Thousand Oaks, CA: Amgen Inc.; February 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 2, 2023.

REMICADE (infliximab)
AVSOLA (infliximab-axxq)
INFLECTRA (infliximab-dyyb)
RENFLEXIS (infliximab-abda)
infliximab

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. infliximab/Avsola/Inflectra/Remicade/Renflexis
      i. Crohn's disease
         a. Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy.
         b. Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD.
      ii. Pediatric Crohn's disease
      Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who have had an inadequate response to conventional therapy.
      iii. Ulcerative colitis
      Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.
      iv. Pediatric ulcerative colitis
      Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active UC who have had an inadequate response to conventional therapy.
      v. Rheumatoid arthritis in combination with methotrexate
      Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA).
      vi. Ankylosing spondylitis
      Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS).
      vii. Psoriatic arthritis
      Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis (PsA).
      viii. Plaque Psoriasis
      Treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis (PsO) who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

B. Compendial Uses
   1. Adult-onset Still's disease
   2. Arthritis in Crohn's disease
   3. Non-radiographic axial spondyloarthritis
   4. Behcet's disease
   5. Gastrointestinal tract transplantation organ rejection
   6. Giant cell arteritis
   7. Acute graft versus host disease
   8. Hidradenitis suppurativa

9. Juvenile idiopathic arthritis
10. Kawasaki disease
11. Necrobiosis lipoidica diabeticorum
12. Polyarteritis nodosa
13. Pyoderma gangrenosum
14. Rheumatoid arthritis as monotherapy
15. Severe, refractory SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome
16. Sarcoidosis
17. Subcorneal pustular dermatosis
18. Synovitis
19. Takayasu's arteritis
20. Uveitis
21. Immune checkpoint inhibitor-related toxicity
22. Multisystem inflammatory syndrome in children (MIS-C)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), psoriatic arthritis (PsA), plaque psoriasis (PsO), adult-onset Still's disease (AOSD), hidradenitis suppurativa, juvenile idiopathic arthritis (JIA), uveitis, and immune checkpoint inhibitor-related inflammatory arthritis

   For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Crohn's disease (CD)
Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

B. Ulcerative colitis (UC)
Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

C. Rheumatoid arthritis (RA)
Authorization of 12 months may be granted for treatment of moderately to severely active rheumatoid arthritis.

D. Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)
Authorization of 12 months may be granted for treatment of active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

E. Psoriatic arthritis (PsA)
Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

F. Plaque psoriasis (PsO)
Authorization of 12 months may be granted for treatment of plaque psoriasis.

G. Adult-onset Still's disease (AOSD)
Authorization of 12 months may be granted for treatment of active adult-onset Still's disease.

H. Arthritis in Crohn's disease (CD)
Authorization of 12 months may be granted for treatment of arthritis in a member with Crohn's disease.

I. Behcet's disease
Authorization of 12 months may be granted for treatment of Behcet's disease.

J. Gastrointestinal tract transplantation organ rejection
Authorization of 6 months may be granted for treatment of gastrointestinal tract transplantation organ rejection.

K. Giant cell arteritis
Authorization of 3 months may be granted for treatment of giant cell arteritis.

L. Acute graft versus host disease
Authorization of 12 months may be granted for treatment of acute graft versus host disease.

M. Hidradenitis suppurativa
Authorization of 12 months may be granted for treatment of hidradenitis suppurativa.

N. Juvenile idiopathic arthritis (JIA)
Authorization of 12 months may be granted for treatment of active juvenile idiopathic arthritis.

O. Kawasaki disease
Authorization of 1 month may be granted for treatment of Kawasaki disease.

P. Necrobiosis lipoidica diabeticorum
Authorization of 12 months may be granted for treatment of necrobiosis lipoidica diabeticorum.

Q. Polyarteritis nodosa
Authorization of 12 months may be granted for treatment of polyarteritis nodosa.

R. Pyoderma gangrenosum
Authorization of 12 months may be granted for treatment of pyoderma gangrenosum.

S. SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome
Authorization of 12 months may be granted for treatment of severe, refractory SAPHO syndrome.

T. Sarcoidosis
Authorization of 12 months may be granted for treatment of sarcoidosis.

U. Subcorneal pustular dermatosis
Authorization of 6 months may be granted for treatment of subcorneal pustular dermatosis.

V. Synovitis
Authorization of 12 months may be granted for treatment of synovitis.

W. Takayasu's arteritis
Authorization of 12 months may be granted for treatment of Takayasu's arteritis.

X. Uveitis
Authorization of 12 months may be granted for treatment of uveitis.

Y. Immune checkpoint inhibitor-related inflammatory arthritis
Authorization of 12 months may be granted for treatment of immune checkpoint inhibitor-related inflammatory arthritis.

Z. Immune checkpoint inhibitor-related toxicity
Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity.

AA. Multisystem inflammatory syndrome in children (MIS-C)

Authorization of 1 month may be granted for treatment of multisystem inflammatory syndrome in children (MIS-C) post severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who have failed to respond to standard pharmacologic therapy.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Crohn's disease (CD) and ulcerative colitis (UC)
Authorization for 12 months may be granted when both of the following criteria are met:
1. The member is currently receiving therapy with Avsola, Inflectra, infliximab, Remicade, or Renflexis.
2. The member is receiving benefit from therapy.

B. Gastrointestinal tract transplantation organ rejection, giant cell arteritis, Kawasaki disease, subcorneal pustular dermatosis, immune checkpoint inhibitor-related toxicity, and multisystem inflammatory syndrome in children (MIS-C)
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

C. All other indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Avsola, Inflectra, infliximab, Remicade, or Renflexis.
2. The requested medication is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for infliximab, Remicade, Avsola, Inflectra, and Renflexis.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
3. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update.
4. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis.
5. EULAR recommendations on management of Behcet's syndrome.
6. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management.
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8. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis.
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10. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association.
11. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa.
12. Etiology and management of pyoderma gangrenosum: a comprehensive review.
13. European Respiratory Society (ERS) clinical practice guidelines on treatment of sarcoidosis.

14. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis.
15. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial.
16. Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents.
17. Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study.
18. A review of systemic biologics and local immunosuppressive medications in uveitis.
19. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders.
20. NCCN guideline: Hematopoietic cell transplantation.
21. NCCN guideline: Management of immunotherapy-related toxicities.
22. COVID-19 Treatment Guidelines Panel: Coronavirus disease 2019 (COVID-19) treatment guidelines.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for infliximab, Remicade, Avsola, Inflectra, and Renflexis are covered in addition to the following:

A. Adult-onset Still's disease
B. Arthritis in Crohn's disease
C. Non-radiographic axial spondyloarthritis
D. Behçet's disease
E. Gastrointestinal tract transplantation organ rejection
F. Giant cell arteritis
G. Acute graft versus host disease
H. Hidradenitis suppurativa
I. Juvenile idiopathic arthritis
J. Kawasaki disease
K. Necrobiosis lipoidica diabeticorum
L. Polyarteritis nodosa
M. Pyoderma gangrenosum
N. Sarcoidosis
O. Subcorneal pustular dermatosis
P. Synovitis
Q. Takayasu's arteritis
R. Uveitis
S. Immune checkpoint inhibitor toxicity
T. Multisystem inflammatory syndrome in children (MIS-C)

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications (Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis) can be found in the manufacturer's prescribing information.

Support for using infliximab for non-radiographic axial spondyloarthritis can be found in the 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. The guidelines recommend that patients who still have active ankylosing spondylitis (AS) despite treatment with NSAIDs, tumor necrosis factor inhibitor (TNFi) such as infliximab are recommended but the guideline does not recommend any particular TNFi.

Support for using infliximab to treat adult-onset Still's disease can be found in two published case series. Kraetsch et al reported adult-onset Still disease (AOSD) appears to favorably respond to treatment with infliximab. In a small, pilot study, 6 patients diagnosed with AOSD (4 with early onset of disease, and 2 with disease durations of 3 and 5 years, respectively) received an initial course of intravenous infusions of infliximab 5 mg/kg, at 0, 2, and 6 weeks. Further treatment with infliximab was given at 6- to 8-week intervals, contingent upon patient response. At the time of study enrollment, all patients had massive polyarthralgia, 5

had polyarthritis, 5 had persistent fever, 5 had a characteristic rash, 5 had persistent leukocytosis, 4 had splenomegaly, and all 6 patients had elevations of erythrocyte sedimentation rate (ESR) and elevated serum concentrations of C-reactive protein. Hyperferritinemia was seen in 3 patients. All patients showed a beneficial response to treatment, with complete resolution of rash, fever, myalgias, and splenomegaly (the latter after 3 treatments); arthralgia/arthritis resolved in 5 of 6 patients. Normalization also occurred in serological markers of disease activity (CRP, ESR, and ferritin concentration) in all patients. Favorable effects of treatment were evident after the first course of treatment with infliximab and were sustained with continuing infliximab treatment at 6-to-8 week intervals, with treatment durations extending from 5 to 28 months. In the 2 patients with long-standing disease of 3- and 5-years duration, swollen joint counts declined from 30 to 3, and from 3 to 0 joints, respectively; tender joint count declined similarly, from 33 to 3 and from 7 to 2 joints, respectively. Infliximab was tolerated well; 1 patient showed a moderate infusion reaction during the second treatment yet was able to resume infliximab therapy after a brief discontinuation of the infusion.
Cavagna et al indicated that infliximab appeared to induce clinical remission in 3 patients with chronically active, treatment-refractory, adult Still Disease (ASD). Each patient had a disease history of between 4- and 7-years duration, during which time they exhibited relapsing or refractory disease despite treatment with NSAIDs, prednisone, methotrexate (n=3), and cyclosporine (n=1). Patients were given intravenous infusions of infliximab 3 mg/kg at weeks 0, 2, 6, and then once every 8 weeks. Infliximab was to be given once every 4 weeks from week 30 thereafter, and methotrexate was maintained throughout the duration of the study. All patients experienced rapid regression of ASD symptoms (arthralgia, cutaneous rash, fever, pharyngitis), accompanied by progressive reductions in serum concentrations of ferritin, C-reactive protein, and erythrocyte sedimentation rate. One patient developed a diffuse, urticarial rash shortly after the fifth infliximab infusion, necessitating withdrawal from therapy at week 22. The 2 remaining patients both experienced brief relapses on weeks 20 and 28; both rapidly regained a state of remission following repeat infusions of infliximab, and continued to receive infliximab beyond 30 weeks, without signs of relapse. These 2 patients also tolerated tapered reductions in prednisone dosing. Neither of the remaining patients showed development of anticardiolipin antibodies, anti-double stranded DNA, or antinuclear antibodies after prolonged treatment.

Support for using infliximab to treat arthritis in Crohn's disease can be found in a case series by Elman et al. Infliximab appeared to be effective in suppressing joint inflammation associated with arthritis secondary to Crohn disease. In a series of case reports, patients with treatment-refractory, joint inflammation associated with long-standing Crohn disease (9 to 31 years duration; n=4) were given intravenous infliximab 5 mg/kg at 8 to 16-week intervals after the initial induction schedule. All patients had prolonged episodes of joint and back pain associated with periods of quiescence in their inflammatory bowel disease; 2 patients had "sausage-shaped" finger and toe swelling, and 3 patients presented with pain in the sacroiliac joint (SI-joint). No patient had radiographic abnormalities of the SI-joint. All patients had been receiving treatment with prednisone up to 40 mg per day, accompanied by 1 or more antiarthritic agents including azathioprine, methotrexate, minocycline, and sulfasalazine. Patients had favorable responses to infliximab, experiencing clinically meaningful reductions in joint pain and swelling, allowing for dose reductions or withdrawals of corticosteroid and antiarthritic agents. One patient discontinued infliximab therapy due to anorexia and insomnia.

Support for Behcet's disease can be found the European League Against Rheumatism (EULAR) recommendations on management of Behcet syndrome (BS). Hatemi and colleagues (2018) noted that several new therapeutic modalities with different mechanisms of action have been studied in patients with BS. These researchers updated the recommendations in the light of these new data under the auspices of EULAR Standing Committee for Clinical Affairs. The recommendations on the medical management of muco-cutaneous, joint, eye, vascular, neurological and GI involvement of BS were modified; 5 overarching principles and a new recommendation about the surgical management of vascular involvement were added. For BS with eye involvement, among the monoclonal anti-TNF antibodies, although there is more accumulated experience with IFX, ADA also appeared to be an effective alternative. Switching between these agents appeared to be possible in patients with primary or secondary unresponsiveness or AEs. Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, IFX or IFN-alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.

Support for using infliximab to treat gastrointestinal tract organ transplantation rejection can be found in two case reports by Pascher et al. In 2 case reports, infliximab was effective in the treatment of steroid and OKT3 (muromonab-CD3)-refractory moderate to severe acute cellular rejection in intestinal transplant recipients. Following either 5 or 10 days of treatment with OKT3 and enhanced baseline immunosuppressive therapy,

acute cellular rejection persisted. Patients were then treated with 3 mg/kg IV infliximab; both patients received 4 infusions, 2 to 4 weeks apart. Improvement was observed within 1 week of the first infusion. Absence of clinical symptoms and histological signs of rejection persisted for at least 8 months for 1 patient and at least 10 months for the other.

Support for using infliximab to treat giant cell arteritis can be found in an open-label case study (Cantini et al). Administration of infliximab was effective in provoking remission in patients with active, steroid-dependent giant cell arteritis (GCA). In an open-label case study, 4 patients with long-standing GCA (disease duration ranging from 42 to 54 months) were unable to tolerate the tapering of their daily corticosteroid dose to less than 12.5 mg. They were given a 3-dose regimen of intravenous infliximab 3 mg/kg, at 0, 2, and 6 weeks, concurrent with reduction of their steroid dose to prednisone 5 mg per day. Three patients experienced a complete response to infliximab therapy, exhibiting both clinical and humeral evidence of remission (resolution of cranial and systemic symptoms, articular symptoms, visual symptoms, and normalization of erythrocyte sedimentation rate and serum concentration of C-reactive protein) after the second dose of infliximab. These responders remained in remission for up to 6 months after the third infliximab infusion, without requiring further treatment with corticosteroid. The fourth patient initially showed a partial response to the first infusion; however, she experienced clinical relapse at the time of her second infusion, causing her to withdraw from the study per the prospectively established protocol. Infliximab was well tolerated by all patients, and adverse events were neither reported nor observed.

Support for hidradenitis suppurativa can be found in the North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management. The guideline indicates infliximab is recommended for moderate-to-severe disease. Dose ranging studies are needed to determine the optimal dosage for management.

Support for juvenile idiopathic arthritis can be found in the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Using infliximab in combination with a DMARD was a strong recommendation despite the low quality of evidence, primarily given more extensive experience with the need for combination therapy to reduce the risk of antidrug antibody formation.

Support for Kawasaki disease can be found in the following document produced by the American Heart Association: Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. A 2-center, randomized, double-blind, placebo-controlled trial of infliximab plus IVIG for intensification of initial treatment enrolled 196 subjects. The study was powered for the primary outcome measure of reducing IVIG resistance from 20% to 5%. Secondary outcome measures included reduction of inflammatory parameters and the change in coronary artery Z scores. Although the number of fever days was shortened and inflammatory parameters normalized more rapidly in the infliximab-treated subjects, the rates of IVIG resistance were identical between the 2 arms. A striking finding was the complete prevention of IVIG infusion reactions in children randomized to the infliximab arm compared with a 13% reaction rate in subjects who received placebo before their IVIG infusion. There was a significant decrease in Z score for the LAD in favor of infliximab. However, there was no difference in the rate of coronary artery aneurysms between the groups, although the study was inadequately powered for this end point. On the basis of current information, addition of infliximab to initial therapy with IVIG is safe but does not prevent recrudescent fever.
A phase I multicenter, randomized, open clinical trial of infliximab (5 mg/kg intravenously over 2 hours) versus a second infusion of IVIG (2 g/kg) was performed to determine the safety, tolerability, and pharmacokinetics of infliximab for rescue therapy for patients who had fever at least 36 hours after the end of the initial IVIG infusion. The study enrolled 24 subjects with IVIG-resistant KD and determined that infliximab was well tolerated in infants and children with KD and that the pharmacokinetics were similar to adults, with circulating levels of the monoclonal antibody detected out to 10 weeks. In the Japanese trial, 20 KD patients resistant to 2 consecutive IVIG infusions (2 g/kg each) were treated with infliximab (5 mg/kg), and an apparent clinical response was achieved in 18 (90%). The 2 unresponsive patients were treated with plasma exchange with resolution of their inflammation. The coronary artery abnormalities detected by echocardiogram all subsequently resolved. There were no adverse reactions attributed to infliximab among the study subjects.

A retrospective review of 2 centers that consistently administered either a second dose of IVIG or infliximab to IVIG-resistant patients suggested that patients receiving infliximab had shorter hospitalization and fewer days

of fever, but coronary artery outcomes and adverse events were similar. On the basis of these retrospective data, infliximab can be considered as an alternative to a second infusion of IVIG for resistant patients.

Support for using infliximab to treat necrobiosis lipoidica diabeticorum can be found in a case report by Kolde et al. Infliximab was an effective treatment for refractory ulcerated necrobiosis lipoidica in a 33-year-old man with diabetes mellitus. The patient received once monthly infusions of infliximab (5 mg/kg) for 2 months. Following treatment with infliximab, clinical improvement was reported, including healing of ulcerations, fading of erythematous infiltration, flattening of the raised margin, and substantial reduction in pain. Improvement of the necrobiosis lipoidica was sustained after the cessation of infliximab. The only reported adverse event was the development of miliary tuberculosis after the second infusion, which was possibly drug-related due to the temporal association with infliximab treatment.

Support for polyarteritis nodosa can be found in the 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa. The guidelines recommend use of tumor necrosis factor inhibitors (TNFi) instead of cyclophosphamide to prevent strokes in patients with clinical manifestations of deficiency of adenosine deaminase 2 (DADA2) associated with polyarteritis nodosa (PAN). In addition, a case report by Matusuo et al. describes a 64-year-old man with a diagnosis of PAN who continually relapsed following treatments of glucocorticoids, methotrexate, cyclophosphamide, rituximab, and tacrolimus. After the fifth relapse, infliximab 5 mg/kg was administered at 0, 2, and 6 weeks, followed by 400 mg every 8 weeks. Clinical symptoms and laboratory values improved dramatically within 3 months of starting infliximab and daily prednisolone dose was tapered to 10 mg.

Support for pyoderma gangrenosum (PG) can be found in a study by Ahronowitz et al. Infliximab, an anti-TNFα monoclonal antibody binding both soluble and membrane-bound TNFα, is the only biologic that has shown efficacy in classic PG in a randomized, double-blind, controlled trial (level I evidence). Thirty patients were given either infliximab 5 mg/kg or placebo. At 2 weeks, 6 of 13 patients in the infliximab group showed improvement in the severity and/or size of ulcers, versus only 1 of 17 in the placebo group. After 2 weeks, the 16 non-responders in the placebo group were switched to infliximab and by week 6, 20 of 29 patients treated with infliximab demonstrated improvement in their PG lesions, with 6 of 29 showing complete resolution. Further studies are needed to determine the efficacy of infliximab in idiopathic PG.

Support for sarcoidosis can be found in the practice guidelines from the European Respiratory Society. The practice guidelines recommend the addition of infliximab to improve and/or preserve forced vital capacity (FVC) and quality of life in patients with symptomatic pulmonary sarcoidosis believed to be at higher risk for future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease. Additionally, the guideline recommends the addition of infliximab (compared to no additional treatment) for patients with cutaneous sarcoidosis who have been treated with glucocorticoids and/or other immunosuppressive agents and have continued cosmetically important active skin disease. In patients with neurosarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) with continued disease, the guidelines suggest adding infliximab.

Support for using infliximab to treat subcorneal pustular dermatosis can be found in a case report by Voightlander et al. Infliximab was effective in producing remission in a 79-year-old woman with treatment-refractory subcorneal pustular dermatosis (Sneddon-Wilkinson disease). The patient presented with disease flare (progressive, widespread erythema and pustular eruptions on the legs, forearms, trunk, and abdomen) that was recalcitrant to treatment with acitretin and methylprednisolone. Intravenous infliximab 5 mg/kg was given as a 2-hour infusion. Within 24 hours of treatment, serum analysis revealed a rapid decline in the number of peripheral granulocytes, accompanied by a decline (to within normal limits) in concentration of C-reactive protein. Complete resolution of pustules occurred within 2 days of infusion, leaving a residual scaling of the affected skin. The patient was able to tolerate the withdrawal of methylprednisolone over 3 days. Disease flare occurred 12 days after the first dose of infliximab; a second infliximab infusion (5 mg/kg) was given, provoking a complete remission within a day of the second treatment. Other than a mild, corticosteroid-responsive relapse, the patient remained in complete remission for a minimum of 6 months while receiving a maintenance therapy regimen of acitretin.

Support for synovitis can be found in a randomized, double-blind, placebo-controlled trial (n=20), significant reductions from baseline in MRI-measured synovitis were seen at 14 weeks and 1 year with infliximab plus methotrexate therapy. Disease Modifying Antirheumatic Drug- or oral corticosteroid-I rheumatoid arthritis

patients with recent symptom onset (less than 12 months) and with metacarpophalangeal joint involvement were randomized to methotrexate 7.5 mg once weekly plus infliximab 3 mg/kg or placebo infusion at 0, 2, 6, and then every 8 weeks. MRI-measured synovitis at week-14 (primary endpoint) and at week-54 (secondary endpoint) from baseline were compared between the infliximab and placebo groups. At week 14, median total synovitis score was significantly lower in the infliximab group (5.5 to 3.4) as compared with the placebo arm (6.2 to 5.9) (p less than 0.05). After 54 weeks, median total synovitis score was significantly lower in the infliximab group (3.8) as compared with the placebo arm (6.6) (p less than 0.05). Adverse effects with infliximab included infusion reaction (n=1), elevated liver function enzyme (n=1), and cutaneous vasculitis (n=1).
Additionally, in a placebo-controlled trial (n=24), infliximab plus methotrexate showed a significant percent reduction in total synovial thickness from baseline at 18 weeks compared with methotrexate alone. Patients with early phase rheumatoid arthritis (less than 2 years mean duration) with a minimum of 2 swollen metacarpophalangeal joints despite methotrexate treatment were randomized to methotrexate (escalating dose) plus infliximab 5 mg/kg or placebo infusion at 0, 2, 6, and then every 8 weeks. After 18 weeks, high frequency ultrasonography showed a 50% median reduction in synovial thickness with the infliximab group as opposed to a 1.2% median increase in synovial thickness in the placebo group (p=0.014).

Support for Takayasu's arteritis can be found in the Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents. According to the recommendations, tumor necrosis factor alpha-inhibiting agents are recommended in patients with persistently active Takayasu Arteritis for 6 months or more, or with 2 or more flares or relapses despite glucocorticoid therapy; this is in addition to 1 or more immunosuppressive agent unless not tolerated or contraindicated.
In a 12-month, multicenter, retrospective study (n=15), infliximab therapy resulted in a response rate of 73% to 87% and significantly reduced corticosteroid use in patients with refractory Takayasu arteritis. Patients (median age, 41 years; range, 17 to 61 years) with Takayasu arteritis (median time from disease onset to infliximab therapy, 37 months; range, 6 to 365 months) that was refractory to other nonsteroid immunosuppressive agents or steroids received infliximab 3 mg/kg (n=5) or 5 mg/kg (n=10) IV every 4 to 8 weeks (median, every 6 weeks). Patients were concomitantly receiving steroids (n=14; median prednisone dose, 20 mg; range, 5 to 35 mg/day) and other nonsteroid immunosuppressive therapies (methotrexate, n=7; azathioprine, n=4) with doses that were not modified in the 3 months before infliximab initiation. After a median follow-up of 43 months (range, 4 to 71 months), overall response (including partial or good response; determined by physician in change and by the presence of clinical and biological activity) was achieved in 87% (n=13/15), 77% (n=10/13), and 73% (n=8/11), respectively, at 3, 6, and 12 months. The percentage of patients with disease activity was significantly decreased from 73% at baseline to 20% at 3 months (p less than 0.005), 31% at 6 months (p less than 0.05), and 27% at 12 months (p less than 0.05). The median prednisone dose also significantly decreased from 20 mg (range, 5 to 35 mg) at baseline to 15 mg (range, 5 to 20 mg) at 3 months (p less than 0.005), 7.5 mg (range, 5 to 18 mg) at 6 months (p less than 0.05), and 6 mg (range, 2.5 to 30 mg) at 12 months (p less than 0.05). Additionally, C-reactive protein was decreased from a median of 30 mg/L (range, 4 to 70 mg/L) at baseline to 5 mg/L (range, 0 to 57 mg/L) at 3 months (p less than 0.05) and 6 mg/L (range, 0 to 50 mg/L) at 6 months (p less than 0.05); however, there was no significant difference from baseline at month 12. Adverse events included acute infusion reactions in 2 patients that led to discontinuation of infliximab therapy.
In a single center retrospective study (n=25), partial or complete remission occurred in 18 of 21 patients who received infliximab therapy for the treatment of refractory Takayasu arteritis. Patients (mean age, 35 years; range, 15 to 64 years; median disease duration, 116 months; range, 39 to 344 months; concurrent nonsteroid immunosuppressive therapy, n=18) with Takayasu arteritis who could not achieve stable remission with the use of low-dose prednisone (less than 10 mg/day) and who had received at least 1 additional immunosuppressive agent received infliximab (n=21) or etanercept (n=9). Five patients who were initially treated with etanercept were switched to infliximab. After a median follow-up of 28 months (range, 2 to 84 months), infliximab therapy (median dose 5 mg/kg IV (range, 4 to 10 mg/kg) every 6 weeks (range, 4 to 8 weeks)) resulted in remission (primary endpoint) in 18 patients (complete remission, n=12; partial remission, n=6). In patients who received either etanercept or infliximab, the median prednisone dose was 19 mg (range, 5 to 50 mg) prior to therapy compared with 0 mg (range, 0 to 30 mg) after therapy; 60% of patients were able to completely discontinue prednisone. Relapse occurred in 12 of the 18 patients who initially achieved remission with infliximab; 6 patients required an increase in the dose of infliximab, and steroid therapy was added in 4 patients. Adverse events that required discontinuation of infliximab therapy included abnormal liver function tests (n=1), primary histoplasmosis in a patient who traveled to an endemic region (n=1), and breast cancer (n=1).

Support for uveitis can be found In the Expert Panel Recommendation for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. A committee of the American Uveitis Society performed a systematic review of literature to generate guidelines for use of these agents in ocular inflammatory conditions. A systematic review of published studies was performed. Recommendations were generated using the Grading of Recommendations Assessment, Development, and Evaluation group criteria. Based on these studies, the expert panel recommends infliximab and adalimumab can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthropathy, and scleritis in patients requiring immunomodulation in patients who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation. Infliximab and adalimumab can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success.

Support for acute graft versus host disease (GVHD) can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of infliximab in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options. Therapy for steroid-refractory acute GVHD is often used in conjunction with the original immunosuppressive agent.

Support for using infliximab to manage immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for the management of immunotherapy-related toxicities supports the use of adding infliximab for the management of the following immunotherapy- related conditions:

1. Myocarditis, as a further intervention if no improvement within 24 to 48 hours of starting high-dose methylprednisolone
2. Mild (G1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin
3. Moderate (G2) and strongly consider for severe (G3-4) diarrhea or colitis
4. Moderate or severe inflammatory arthritis as additional disease modifying antirheumatic drug (DMARD) therapy if no improvement after holding immunotherapy and treating with oral corticosteroids or if unable to taper corticosteroids, or no response to conventional synthetic DMARDs
5. G1-4 uveitis that is refractory to high-dose systemic corticosteroids
6. Moderate (G2) pneumonitis if no improvement after 48-72 hours of corticosteroids or severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone
7. Stage 3 acute kidney injury/elevated serum creatinine if toxicity remains more than stage 2 after four to six weeks of corticosteroids or if creatinine increases during steroid taper (once off steroids).

Support for the use of infliximab to treat multisystem inflammatory syndrome in children (MIS-C) can be found in the COVID-19 Treatment Guidelines Panel: Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health (NIH). In pediatric patients hospitalized with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 (COVID19), initial first line treatment is IV immune globulin with low to moderate dose glucocorticoids, such as methylprednisolone (recommendation rating, A; evidence rating, based on nonrandomized trials or observation cohort studies) and should be used in most patients (level of consensus, moderate). The risks versus benefits of treating immunocompromised MIS-C patients with immunomodulatory agents should be evaluated on an individual basis.
If MIS-C is refractory (no improvement within 24 hours of IV immune globulin and steroid initiation), initiate intensification immunomodulatory therapy (recommendation rating, A; evidence rating, expert opinion) (level of consensus, moderate) with higher-dose glucocorticoids, anakinra, or infliximab (recommendation rating, B; evidence rating, based on nonrandomized trials or observation cohort studies) (level of consensus, moderate). Infliximab should not be used in patients with MIS-C and features of macrophage activation syndrome (MAS) (level of consensus, moderate).
Severe illness may warrant dual therapy with higher-dose glucocorticoids plus anakinra (recommendation rating, B; evidence rating, expert opinion), or higher-dose glucocorticoids plus infliximab (recommendation rating, B; evidence rating, expert opinion). Anakinra and infliximab should not be given in combination. Infliximab can be considered in patients with contraindications to long-term use of glucocorticoids (level of consensus, moderate). The effects of infliximab likely persist for weeks, which may provide a steroid-sparing effect.

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ISTODAX (romidepsin)
romidepsin (generic)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Istodax is indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy.

B. Compendial Uses
1. Mycosis fungoides (MF)/Sézary syndrome (SS)
2. Peripheral T-Cell Lymphoma (PTCL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous T-cell lymphoma (CTCL)
Authorization of 12 months may be granted for treatment of CTCL (e.g., mycosis fungoides, Sézary syndrome, primary cutaneous anaplastic large cell lymphoma).

B. Peripheral T-cell lymphoma (PTCL) (see Appendix)
Authorization of 12 months may be granted for treatment of PTCL.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. APPENDIX: PTCL subtypes

1. Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)
2. Angioimmunoblastic T-cell lymphoma (AITL)
3. Anaplastic large cell lymphoma (ALCL)
4. Breast Implant-Associated anaplastic large cell lymphoma (BIA-ALCL)
5. Enteropathy-associated T-cell lymphoma (EATL)
6. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
7. Nodal peripheral T-cell lymphoma with TFH phenotype (PTCL, TFH)
8. Follicular T-cell lymphoma (FTCL)
9. Extranodal NK/T-cell lymphoma (ENKL)
10. Hepatosplenic T-cell lymphoma (HSTCL)

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Istodax.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: T-Cell Lymphoma
4. NCCN Guideline: Primary Cutaneous Lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Istodax are covered in addition to mycosis fungoides (MF)/sézary syndrome (SS) and peripheral T-cell lymphoma (PTCL).

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Istodax to treat mycosis fungoides (MF)/sézary syndrome (SS) and peripheral t-cell lymphoma (PTCL) can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

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2. Romidepsin [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; December 2021.
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Intravenous Immune Globulin (IVIG):

Alyglo, Asceniv, Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga and Privigen

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Primary immunodeficiency
2. Idiopathic thrombocytopenic purpura (ITP)
3. Chronic inflammatory demyelinating polyneuropathy
4. Multifocal motor neuropathy
5. Kawasaki syndrome
6. B-cell chronic lymphocytic leukemia (CLL)
7. Dermatomyositis

B. Compendial Uses
1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy
2. Acquired thrombocytopenia
3. Antiphospholipid syndrome
4. Asthma
5. Autoimmune hemolytic anemia
6. Autoimmune neutropenia
7. Bone marrow transplant/hematopoietic stem cell transplant
8. Cerebellar ataxia due to Epstein-Barr virus infection
9. Clostridium difficile colitis
10. Adjunct to Crohn's disease treatment
11. Cytomegalovirus treatment and prophylaxis
12. Desensitization therapy – heart transplant
13. Diabetic amyotrophy
14. Hopkins' syndrome
15. Acute disseminated encephalomyelitis
16. Prophylaxis of enteritis due to rotavirus
17. Epilepsy
18. Gastroenteritis
19. Granulomatosis with polyangiitis
20. Guillain-Barre syndrome
21. Hemolytic disease of fetus or newborn due to RhD isoimmunization, prophylaxis
22. Hemophagocytic syndrome
23. Induction of Factor VIII immune tolerance
24. Measles (Rubeola) prophylaxis
25. Moderate and severe immune checkpoint inhibitor-related toxicities
26. Hypogammaglobulinemia from CAR-T therapy
27. Herpes gestationis
28. Prevention of bacterial infections in HIV infected patients
29. Prevention of bacterial infections in post-surgical or ICU patients
30. Isaacs syndrome
31. Japanese encephalitis virus disease
32. Severe IgA nephropathy
33. Lambert-Eaton myasthenic syndrome
34. Linear IgA dermatosis
35. Lysinuric protein intolerance
36. Prevention of bacterial infections in patients with multiple myeloma

37. Multiple sclerosis
38. Myasthenia gravis
39. Myocarditis
40. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
41. Neonatal jaundice
42. Otitis media
43. Paraneoplastic visual loss
44. Polyarteritis nodosa
45. Polymyositis
46. Post-transplant lymphoproliferative disorder
47. Pure red cell aplasia
48. Pyoderma gangrenosum
49. Renal transplant rejection
50. Respiratory syncytial virus infection
51. Sepsis
52. Stevens-Johnson syndrome
53. Stiff-person syndrome
54. Systemic lupus erythematosus
55. Systemic onset juvenile chronic arthritis
56. Systemic vasculitis
57. Tetanus treatment and prophylaxis
58. Fetal or neonatal thrombocytopenia
59. Toxic epidermal necrolysis
60. Toxic necrotizing fasciitis
61. Toxic shock syndrome
62. Heart transplant rejection
63. Desensitization of highly sensitized patients awaiting renal transplantation
64. Uveitis
65. Varicella prophylaxis
66. Von Willebrand disorder

C. Nationally Covered Indication
Centers for Medicare and Medicaid Services guidelines provide coverage for IG for the following autoimmune mucocutaneous conditions pursuant to the criteria in Section III:
1. Pemphigus vulgaris
2. Pemphigus foliaceus
3. Bullous pemphigoid
4. Mucous membrane pemphigoid (cicatricial pemphigoid)
5. Epidermolysis bullosa acquisita

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions (where applicable):
A. Myasthenia gravis
   1. Clinical records describing standard treatments tried and failed
B. Secondary hypogammaglobulinemia (e.g., CLL, BMT/HSCT recipients)
   1. Copy of laboratory report with pre-treatment serum IgG level
C. Multifocal motor neuropathy (MMN)
   1. Pre-treatment electrodiagnostic studies (electromyography [EMG] or nerve conduction studies [NCS])
D. Dermatomyositis and polymyositis
   1. Clinical records describing standard treatments tried and failed
E. Lambert-Eaton Myasthenic Syndrome (LEMS)
   1. Neurophysiology studies (e.g., electromyography)
   2. A positive anti- P/Q type voltage-gated calcium channel antibody test
F. Idiopathic thrombocytopenic purpura

1. Laboratory report with pre-treatment/current platelet count
2. Chronic/persistent ITP: copy of medical records supporting trial and failure with corticosteroid or anti-D therapy (unless contraindicated)

G. Stiff-person syndrome
1. Anti-glutamic acid decarboxylase (GAD) antibody testing results
2. Clinical records describing standard treatments tried and failed

H. Toxic shock syndrome or toxic necrotizing fasciitis due to group A streptococcus
1. Documented presence of fasciitis (toxic necrotizing fasciitis due to group A streptococcus only)
2. Microbiological data (culture or Gram stain)

III. CRITERIA FOR INITIAL APPROVAL- HOME ADMINISTRATION

Primary Immune Deficiency Disorder
Authorization of 6 months may be granted for treatment of primary immune deficiency disorder when the following criteria are met:

A. The requested intravenous immune globulin preparation will be administered in the home with an infusion pump.
B. The treating practitioner has determined that administration of the requested intravenous immune globulin in the member's home is medically necessary and appropriate.
C. The member has a primary immune deficiency disorder and has one of the following ICD-10 codes as their diagnosis: D80.0 (hereditary hypogammaglobulinemia), D80.2 (selective deficiency of immunoglobulin A), D80.3 (selective deficiency of immunoglobulin G subclasses), D80.4 (selective deficiency of immunoglobulin M), D80.5 (immunodeficiency with increased immunoglobulin M), D80.6 (antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia), D80.7 (transient hypogammaglobulinemia of infancy), D81.0 (severe combined immunodeficiency [SCID] with reticular dysgenesis), D81.1 (SCID with low T- and B-cell numbers), D81.2 (SCID with low or normal B-cell numbers), D81.5 (purine nucleoside phosphorylase deficiency), D81.6 (major histocompatibility complex class I deficiency), D81.7 (major histocompatibility complex class II deficiency), D81.82 (activated phosphoinositide 3-kinase delta syndrome), D81.89 (other combined immunodeficiencies), D81.9 (combined immunodeficiency, unspecified), D82.0 (Wiskott-Aldrich syndrome), D82.1 (Di George's syndrome), D82.4 (hyperimmunoglobulin E syndrome), D83.0 (common variable immunodeficiency with predominant abnormalities of B-cell numbers and function), D83.1 (common variable immunodeficiency with predominant immunoregulatory T-cell disorders), D83.2 (common variable immunodeficiency with autoantibodies to B- or T-cells), D83.8 (other common variable immunodeficiencies), D83.9 (common variable immunodeficiency, unspecified), G11.3 (cerebellar ataxia with defective DNA repair).

IV. CRITERIA FOR INITIAL APPROVAL

A. Primary immunodeficiency
Initial authorization of 6 months may be granted for members with primary immunodeficiency.

B. Myasthenia gravis
1. Authorization of 1 month may be granted to members who are prescribed IG for worsening weakness, acute exacerbation, or in preparation for surgery.[22-24]
   a. Worsening weakness includes an increase in any of the following symptoms: diplopia, ptosis, blurred vision, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), difficulty chewing, impaired respiratory status, fatigue, and limb weakness. Acute exacerbations include more severe swallowing difficulties and/or respiratory failure
   b. Pre-operative management (e.g., prior to thymectomy)
2. Authorization of 6 months may be granted to members with refractory myasthenia gravis who have tried and failed 2 or more standard therapies (e.g., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, rituximab).

C. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
Authorization of 3 months may be granted for treatment of chronic inflammatory demyelinating polyneuropathy.

D. Dermatomyositis or Polymyositis

Authorization of 3 months may be granted when the following criteria are met:

1. Member has at least 4 of the following:
    a. Proximal muscle weakness (upper or lower extremity and trunk)
    b. Elevated serum creatine kinase (CK) or aldolase level
    c. Muscle pain on grasping or spontaneous pain
    d. Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials)
    e. Positive for anti-synthetase antibodies (e.g., anti-Jo-1, also called histadyl tRNA synthetase)
    f. Non-destructive arthritis or arthralgias
    g. Systemic inflammatory signs (fever: more than 37°C at axilla, elevated serum CRP level or accelerated ESR of more than 20 mm/h by the Westergren method),
    h. Pathological findings compatible with inflammatory myositis (inflammatory infiltration of skeletal evidence of active regeneration may be seen), and
2. Standard first-line treatments (corticosteroids) and second-line treatments (immunosuppressants) have been tried but were unsuccessful or not tolerated, or
3. Member is unable to receive standard first-line and second-line therapy because of a contraindication or other clinical reason.

E. Idiopathic Thrombocytopenic Purpura (ITP)/Immune Thrombocytopenia

1. Newly diagnosed ITP (diagnosed within the past 3 months) or initial therapy: authorization of 1 month may be granted when the following criteria are met:
    a. Children (< 18 years of age)
        i. Significant bleeding symptoms (mucosal bleeding or other moderate/severe bleeding) or
        ii. High risk for bleeding* (see Appendix B), or
        iii. Rapid increase in platelets is required* (e.g., surgery or procedure)
    b. Adults (≥ 18 years of age)
        i. Platelet count < 30,000/mcL, or
        ii. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required*, and
        iii. Corticosteroid therapy is contraindicated and IG will be used alone or IG will be used in combination with corticosteroid therapy
2. Chronic/persistent ITP (≥ 3 months from diagnosis) or ITP unresponsive to first-line therapy: authorization of 6 months may be granted when the following criteria are met:
    a. Platelet count < 30,000/mcL, or
    b. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding* or rapid increase in platelets is required*, and
    c. Relapse after previous response to IG or inadequate response/intolerance/contraindication to corticosteroid or anti-D therapy
3. Adults with refractory ITP after splenectomy: authorization of 6 months may be granted when either of the following criteria is met:
    a. Platelet count < 30,000/mcL, or
    b. Significant bleeding symptoms
4. ITP in pregnant women: authorization through delivery may be granted to pregnant women with ITP.

    * The member's risk factor(s) for bleeding (see Appendix B) or reason requiring a rapid increase in platelets must be provided.

F. B-cell chronic lymphocytic leukemia (CLL)

Authorization of 6 months may be granted for treatment of B-cell chronic lymphocytic leukemia (CLL) when all of the following criteria are met:

1. IG is prescribed for prophylaxis of bacterial infections.
2. Member has a history of recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.
3. Member has a pretreatment serum IgG level <500 mg/dL.

G. Bone marrow transplant/hemopoietic stem cell transplant (BMT/HSCT)

Authorization of 6 months may be granted to members who are BMT/HSCT recipients when the following criteria are met:

a. Therapy will be used to prevent the risk of acute graft-versus-host disease, associated interstitial pneumonia (infectious or idiopathic), septicemia, and other infections (e.g., cytomegalovirus infections [CMV], recurrent bacterial infection).
b. Either of the following:
    i. IG is requested within the first 100 days post-transplant.
    ii. Member has a pretreatment serum IgG < 400 mg/dL

H. Multifocal Motor Neuropathy (MMN)

Authorization of 3 months may be granted for treatment of multifocal motor neuropathy when the following criteria are met:

1. Member experienced progressive, multifocal, asymmetrical weakness without objective sensory loss in 2 or more nerves for at least 1 month
2. The diagnosis was confirmed by electrodiagnostic studies

I. Guillain-Barre syndrome (GBS)

Authorization of 1 month total may be granted for GBS when the following criteria are met:

1. Member has severe disease with significant weakness (e.g., inability to stand or walk without aid, respiratory weakness)
2. Onset of neurologic symptoms occurred less than 4 weeks from the anticipated start of therapy

J. Lambert-Eaton myasthenic syndrome (LEMS)

Authorization of 6 months may be granted for LEMS when the following criteria are met:

1. Diagnosis has been confirmed by either of the following:
    a. Neurophysiology studies (e.g., electromyography)
    b. A positive anti- P/Q type voltage-gated calcium channel antibody test
2. Anticholinesterases (e.g., pyridostigmine) and amifampridine (e.g., 3,4-diaminopyridine phosphate, Firdapse) have been tried but were unsuccessful or not tolerated
3. Weakness is severe or there is difficulty with venous access for plasmapheresis

K. Kawasaki syndrome

Authorization of 1 month may be granted for treatment of Kawasaki syndrome in pediatric patients.

L. Stiff-person syndrome

Authorization of 6 months may be granted for stiff-person syndrome when the following criteria are met:

1. Diagnosis has been confirmed by anti-glutamic acid decarboxylase (GAD) antibody testing
2. Member had an inadequate response to first-line treatment (benzodiazepines and/or baclofen)

M. Moderate and severe immune checkpoint inhibitor-related toxicities

Authorization of 1 month may be granted for management of immune checkpoint-inhibitor toxicities when all of the following criteria are met:

1. Member has experienced a moderate or severe adverse event to a PD-1 or PD-L1 inhibitor (e,g., pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab)
2. The offending medication has been held or discontinued
3. Member experienced one or more of the following adverse events: myocarditis, bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, myasthenia gravis, peripheral neuropathy, encephalitis, transverse myelitis, severe inflammatory arthritis, Guillain-Barre syndrome, or steroid-refractory myalgias or myositis

N. Acute disseminated encephalomyelitis

Authorization of 1 month may be granted for acute disseminated encephalomyelitis in members who have had an insufficient response or a contraindication to intravenous corticosteroid treatment.

O. Autoimmune mucocutaneous blistering disease

Authorization of 6 months may be granted for treatment of biopsy proven autoimmune mucocutaneous blistering diseases when all of the following criteria are met:

1. Member has one of the following diagnoses: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (cicatricial pemphigoid), or epidermolysis bullosa acquisita.
2. At least one of the following criteria is met regarding prior treatment with conventional therapy:

a. Member has failed conventional therapy
b. Member has a contraindication to conventional therapy
c. Member has rapidly progressive disease and a clinical response could not be affected quickly enough using conventional agents, and IG will be given in combination with conventional treatment.

3. IG will be used for short-term control of the member's condition and will not be used as maintenance therapy.

P. Autoimmune hemolytic anemia
Authorization of 6 months may be granted for treatment of autoimmune hemolytic anemia in members who do not respond or have a contraindication to corticosteroids or splenectomy.

Q. Autoimmune neutropenia
Authorization of 6 months may be granted for treatment of autoimmune neutropenia where treatment with G-CSF (granulocyte colony stimulating factor) is not appropriate.

R. Acquired Thrombocytopenia
Authorization of 1 month may be granted for acquired thrombocytopenia.

S. Prevention of bacterial infections in patients with multiple myeloma
Authorization of 6 months may be granted for multiple myeloma in members who have recurrent, serious infections despite the use of prophylactic antibiotics.

T. Japanese encephalitis virus disease
Authorization of 1 month may be granted for Japanese encephalitis virus disease

U. Measles (Rubeola) prophylaxis
Authorization of 1 month may be granted for postexposure prophylaxis to prevent or modify symptoms of measles (rubeola) in susceptible members exposed to the disease less than 6 days previously.

V. Multiple sclerosis
Authorization of 6 months may be granted for treatment of relapsing-remitting multiple sclerosis (RRMS).

W. Stevens-Johnson syndrome
Authorization of 1 month may be granted for severe cases of Stevens-Johnson syndrome

X. Tetanus treatment and prophylaxis
Authorization of 1 month may be granted for treatment or postexposure prophylaxis of tetanus as an alternative when tetanus immune globulin (TIG) is unavailable.

Y. Toxic epidermal necrolysis
Authorization of 1 month may be granted for severe cases of toxic epidermal necrolysis

Z. Toxic shock syndrome
Authorization of 1 month may be granted for staphylococcal or streptococcal toxic shock syndrome when the infection is refractory to several hours of aggressive therapy, an undrainable focus is present, or the member has persistent oliguria with pulmonary edema.

AA. Systemic lupus erythematosus (SLE)
Authorization of 6 months may be granted for severe, active SLE in members who have experienced inadequate response, intolerance or have a contraindication to first and second line therapies (e.g., hydroxychloroquine, glucocorticoids, anifrolumab, rituximab).

BB. Toxic Necrotizing Fasciitis Due To Group A Streptococcus
Authorization of 1 month may be granted for members with fasciitis due to invasive streptococcal infection

CC. Varicella prophylaxis

Authorization of 1 month may be granted for postexposure prophylaxis of varicella in susceptible individuals when varicella-zoster immune globulin (VZIG) is unavailable.

DD. Other indications

Authorization of 6 months may be granted for the following indications:

1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy or CAR-T therapy
2. Antiphospholipid syndrome
3. Asthma
4. Cerebellar ataxia due to Epstein-Barr virus infection
5. Clostridium difficile colitis
6. Adjunct to Crohn's disease treatment
7. Cytomegalovirus treatment and prophylaxis when the member is undergoing a transplant
8. Desensitization therapy – heart transplant
9. Diabetic amyotrophy
10. Hopkins' syndrome
11. Prophylaxis of enteritis due to rotavirus
12. Epilepsy
13. Fetal or neonatal thrombocytopenia
14. Gastroenteritis
15. Granulomatosis with polyangiitis
16. Hemolytic disease of fetus or newborn due to RhD isoimmunization
17. Hemophagocytic syndrome
18. Induction of Factor VIII immune tolerance
19. Herpes gestationis
20. Prevention of bacterial infections in HIV infected patients
21. Prevention of bacterial infections in post-surgical or ICU patients
22. Isaacs syndrome
23. Severe IgA nephropathy
24. Linear IgA dermatosis
25. Lysinuric protein intolerance
26. Myocarditis
27. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
28. Neonatal jaundice
29. Otitis media
30. Paraneoplastic visual loss
31. Polyarteritis nodosa
32. Post-transplant lymphoproliferative disorder
33. Pure red cell aplasia
34. Pyoderma gangrenosum
35. Renal transplant rejection
36. Respiratory syncytial virus infection
37. Sepsis
38. Systemic onset juvenile chronic arthritis
39. Systemic vasculitis
40. Heart transplant rejection
41. Desensitization of highly sensitized patients awaiting renal transplantation
42. Uveitis
43. Von Willebrand disorder

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Acquired Thrombocytopenia, Acute disseminated encephalomyelitis, Guillain-Barre syndrome, Japanese encephalitis virus disease, Kawasaki syndrome, Measles prophylaxis, Moderate and severe immune checkpoint inhibitor-related toxicities, Steven's Johnson syndrome, Tetanus

treatment and prophylaxis, Toxic epidermal necrolysis, Toxic shock syndrome, Toxic Necrotizing Fasciitis Due To Group A Streptococcus, Varicella prophylaxis
Authorization for members who are requesting authorization for continuation of therapy of IG must meet all initial authorization criteria.

B. Primary Immune Deficiency
Authorization of 12 months may be granted when ALL of the following criteria are met:
1. The member is currently receiving therapy with IG
2. The member is receiving benefit from therapy, such as a reduction in the frequency of infections, improvement in disability, stabilization of condition.

C. All other indications
Authorization of 6 months may be granted when ALL of the following criteria are met:
1. The member is currently receiving therapy with IG
2. IG is being used to treat an indication enumerated in Section III
3. The member is receiving benefit from therapy, such as a reduction in the frequency of infections, improvement in disability, stabilization of condition.

VI. APPENDICES

Appendix A: Impaired Antibody Response to Pneumococcal Polysaccharide Vaccine
- Age 2 years and older: impaired antibody response demonstrated to vaccination with a pneumococcal polysaccharide vaccine
- Not established for children less than 2 years of age
- Excludes the therapy initiated in the hospital setting

Appendix B: Examples of Risk Factors for Bleeding (not all inclusive)
- Undergoing a medical or dental procedure where blood loss is anticipated
- Comorbidity (e.g., peptic ulcer disease, hypertension)
- Mandated anticoagulation therapy
- Profession or lifestyle predisposes patient to trauma (e.g., construction worker, fireman, professional athlete)

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Alyglo, Asceniv, Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga, and Privigen
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Chronic lymphocytic leukemia/Small lymphocytic lymphoma
4. NCCN Guideline: Management of immunotherapy-related toxicities
5. Update on the use of immunoglobulin in human disease: a review of evidence by Work Group Report of the American Academy of Allergy, Asthma, and Immunology.
6. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services.
7. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective.
8. Guidelines on the use of intravenous immune globulin for neurologic conditions.
9. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee.

10. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases.
11. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.
12. Guidelines on the use of intravenous immune globulin for hematologic conditions.
13. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency
14. Practice parameter for the diagnosis and management of primary immunodeficiency.
15. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest section of the American Academy of Allergy, Asthma and Immunology.
16. European Society for Immunodeficiencies. Diagnostic criteria for Primary Immune Deficiency (PID).
17. Immune Deficiency Foundation. *Diagnostic and Clinical Care Guidelines for Primary Immunodeficiency Diseases*. 3rd edition.
18. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – second revision.
19. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Societies guideline on management of multifocal motor neuropathy
20. Consensus criteria for the diagnosis of multifocal motor neuropathy.
21. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia.
22. Updated international consensus report on the investigation and management of primary immune thrombocytopenia.
23. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience
24. Working Group on Antiretroviral Therapy of the National Pediatric HIV Resource Center. Antiretroviral therapy and medical management of pediatric HIV infection
25. Center for Medicare and Medicaid Services (CMS). Intravenous immune globulin for autoimmune mucocutaneous blistering diseases. Decision Memorandum.
26. Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA)Consensus Task Force recommendations for evaluation and management.
27. Staphylococcus aureus. American Academy of Pediatrics. Red Book: 2018 Report of the Committee on Infectious Diseases.
28. British Society for Rheumatology guideline on management of systemic lupus erythematosus in adults
29. Guidelines on the use of intravenous immune globulin for hematologic conditions.
30. Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care.
31. European Guidelines (S1) on the use of high-dose intravenous immunoglobulin in dermatology
32. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock
33. British Association of Dermatologists' guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people
34. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus.
35. NCD 250.3: Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Alyglo, Asceniv, Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga, and Privigen are covered in addition to the following:

1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy
2. Acquired thrombocytopenia
3. Antiphospholipid syndrome
4. Asthma
5. Autoimmune hemolytic anemia
6. Autoimmune neutropenia
7. Bone marrow transplant/hematopoietic stem cell transplant
8. Cerebellar ataxia due to Epstein-Barr virus infection

9. Clostridium difficile colitis
10. Adjunct to Crohn's disease treatment
11. Cytomegalovirus treatment and prophylaxis
12. Desensitization therapy – heart transplant
13. Dermatomyositis
14. Diabetic amyotrophy
15. Hopkins' syndrome
16. Acute disseminated encephalomyelitis
17. Prophylaxis of enteritis due to rotavirus
18. Epilepsy
19. Gastroenteritis
20. Granulomatosis with polyangiitis
21. Guillain-Barre syndrome
22. Hemolytic disease of fetus or newborn due to RhD isoimmunization, prophylaxis
23. Hemophagocytic syndrome
24. Induction of Factor VIII immune tolerance
25. Measles (Rubeola) prophylaxis
26. Moderate and severe immune checkpoint inhibitor-related toxicities
27. Hypogammaglobulinemia from CAR-T therapy
28. Herpes gestationis
29. Prevention of bacterial infections in HIV infected patients
30. Prevention of bacterial infections in post-surgical or ICU patients
31. Isaacs syndrome
32. Japanese encephalitis virus disease
33. Severe IgA nephropathy
34. Lambert-Eaton myasthenic syndrome
35. Linear IgA dermatosis
36. Lysinuric protein intolerance
37. Prevention of bacterial infections in patients with multiple myeloma
38. Multiple sclerosis
39. Myasthenia gravis
40. Myocarditis
41. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
42. Neonatal jaundice
43. Otitis media
44. Paraneoplastic visual loss
45. Polyarteritis nodosa
46. Polymyositis
47. Post-transplant lymphoproliferative disorder
48. Pure red cell aplasia
49. Pyoderma gangrenosum
50. Renal transplant rejection
51. Respiratory syncytial virus infection
52. Sepsis
53. Stevens-Johnson syndrome
54. Stiff-person syndrome
55. Systemic lupus erythematosus
56. Systemic onset juvenile chronic arthritis
57. Systemic vasculitis
58. Tetanus treatment and prophylaxis
59. Fetal or neonatal thrombocytopenia
60. Toxic epidermal necrolysis
61. Toxic necrotizing fasciitis
62. Toxic shock syndrome
63. Heart transplant rejection
64. Desensitization of highly sensitized patients awaiting renal transplantation
65. Uveitis
66. Varicella prophylaxis
67. Von Willebrand disorder
68. Idiopathic thrombocytopenic purpura (ITP)

69. Multifocal motor neuropathy
70. Kawasaki syndrome
71. B-cell chronic lymphocytic leukemia (CLL)

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.
This policy considers subcutaneous administration of immune globulin as an alternative to intravenous therapy and intramuscular therapy in members who meet medical necessity criteria for intravenous immune globulin or intramuscular immune globulin.

Support for using immune globulin to treat acquired thrombocytopenia can be found in a several small studies. Hartert and colleagues reported that intravenous immune globulin provided a sustained response in a man with severe thrombocytopenia following a mismatched, related allogeneic stem cell transplant (SCT). Nine months after SCT, the man presented with papular cutaneous lesions, diarrhea, and pancytopenia. Tests for cytomegalovirus were positive. Within a few days he developed fever, arthralgia, severe pancytopenia, generalized edema, polyserositis with pericardial and pleural effusions, and nephrotic syndrome. Skin and bowel symptoms were interpreted as graft-versus-host disease. Anemia was refractory to red cell transfusion. Autoantibody testing suggested a lupus-like syndrome. He was treated with prednisolone and mycophenolate mofetil (MMF) before IVIG treatment was begun at 0.4 mg/kg on 5 consecutive days. A total of 4 cycles were given. At 2 months after symptom onset, his renal function had improved, and body weight had normalized. Hemoglobin (Hb) and platelet count were still low at the time of discharge, but there were no clinical signs of anemia or bleeding. Several weeks later, the patient was readmitted with arthralgia and decreases in platelet count and Hb associated with a slight reduction in steroid therapy. Cytomegalovirus tests were again positive, and he was treated with foscarnet and ganciclovir. IVIG was given at 0.4 mg/kg for 5 days, resulting in a marked increase in platelet count. Hb rose slowly after discharge. IVIG was repeated 2 weeks later at a reduced dose of 5 g/day for 5 days and repeated every 4 weeks thereafter. Hb stabilized at greater than 9 g/dL, and the platelet count was maintained at greater than 80 x 10(9)/liter. The patient had no signs of graft-versus-host disease. He continued immunosuppressive therapy with prednisolone 3 mg/day and MMF 750 mg/day.
Chute et al treated trimethoprim-sulfamethoxazole thrombocytopenia in a 21-year-old patient with intravenous immune globulin (IVIG) treatment. The patient did not respond to methylprednisolone and was treated with IVIG 0.4 g/kg and a platelet transfusion. Within 1 hour, resolution of the acutely progressive disorder was measured. The proposed mechanism is an immunoglobulin-mediated reticuloendothelial Fc receptor blockade.
Guzzi et al used IVIG 0.2 g/kg for 7 days, in combination with corticosteroids, to treat secondary thrombocytopenia to sarcoidosis in a 22-year-old male. Corticosteroids alone were not effective; the platelet count did not increase substantially until IV immune globulin was added to therapy.

Support for using immune globulin to treat antiphospholipid syndrome can be found in a study by Gordon and Kilby. Therapy with intravenous immune globulin 2 g/kg in divided doses over 2 to 5 days resulted in marked clinical benefits in 4 pregnant patients (including one twin pregnancy) who developed, in the second half of pregnancy, intrauterine growth restriction (IUGR) associated with systemic lupus erythematosus and/or antiphospholipid syndrome. There were 2 early date fetal deaths. All pregnant patients had been receiving aspirin and high-dose subcutaneous heparin in the second trimester.

Support for using immune globulin to treat asthma can be found in a study by Salmun et al. Therapy with intravenous immune globulin (IVIG) 400 mg/kg every 3 weeks significantly decreased the oral steroid required by 9 patients with severe asthma that participated in a double-blind, placebo-controlled, randomized trial over 9 months. The median oral steroid required after IVIG went down to 3 mg/day from a median dose of 16.4 mg/day before IVIG treatment (p=0.0078).
Mazer and Gelfand investigated the use of IVIG in pediatric patients with asthma. Immune globulin was found to reduce the dose of corticosteroids needed and improve pulmonary function tests and symptoms in 8 children with asthma. The dose of immune globulin was 1 g/kg/day for 2 consecutive days repeated every 4 weeks for 6 months.

Support for using immune globulin to treat autoimmune hemolytic anemia can be found in a study by Flores et al (1993). Of 72 patients with warm-antibody autoimmune hemolytic anemia, approximately 40% responded to

intravenous immune globulin (IVIG) treatment. Those with hepatomegaly and a low pretreatment hemoglobin had the best response to IVIG. The investigators suggest IVIG as adjunctive treatment only in select cases.

Support for using immune globulin to treat autoimmune neutropenia can be found in guidelines for the use of intravenous immune globulin for hematologic conditions from the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services. In general, immune globulin is not recommended for routine care but can be used in life-threatening circumstances.

Support for using immune globulin in patients who have received bone marrow transplants or hematopoietic stem cell transplants can be found in several published studies. A meta-analysis published by Bass et al (1993) found IVIG prophylaxis was associated with a significant reduction in posttransplant complications. Winston et al (1993) found IVIG reduces the incidence and severity of graft versus host disease. The recommended dose of immune globulin is 500 mg/kg IV 7 days and 2 days before transplantation, then weekly for 90 days following the transplant. Abdel-Mageed and colleagues (1999) conducted a comparison of two doses of intravenous immune globulin (IVIG), 250 mg/kg or 500 mg/kg given weekly from day -8 to day +111, the higher dose was associated with less acute graft-versus-host disease (p=0.03).

Support for using immune globulin to treat cerebellar ataxia due to Epstein-Barr infection can be found in a study by Daaboul, Vern, and Blend (1998). Intravenous immune globulin (IVIG) dosed at 2 g/kg over 3 days (total 144 g) may have contributed to the recovery of a 19-year-old male with acute post-infectious (Epstein-Barr virus or EBV) cerebellar ataxia. The patient presented with nausea, vomiting, unsteady gait and cervical lymphadenopathy. The presence of anti-EBV capsid IgM antibody, elevated serum EBV IgG antibody and cerebellar hyperperfusion on single-photon emission tomography led to the diagnosis. Within 2 weeks of empiric initiation of IVIG therapy, the patient recovered completely.

Support for using immune globulin to treat clostridium difficile colitis can be found in a study by Leung et al. Intravenous immune globulin was shown to be effective in preventing recurrence of colitis induced by Clostridium difficile toxin in 5 children. C difficile produces 2 types of exotoxin: toxin A and toxin B; toxin A produces diarrhea. These children, with chronically recurrent C difficile-induced colitis were found to have lower circulating levels of antitoxin A immunoglobulins than normal subjects. Administration of IV immune globulin 400 mg/kg every 3 weeks promoted resolution of gastrointestinal symptoms of colitis in all patients. However, colitis recurred in 1 patient after discontinuing the IV immune globulin; therapy was not interrupted in the other patients.

Support for using immune globulin as an adjunct to Crohn’s disease treatment can be found in a study by Knoflach, Muller, and Eible (1990). The study reported transient improvement in the symptoms of Crohn disease in six patients after administration of IV immune globulin 400 mg/kg/day for 5 days. A reduction in abdominal pain and loss of fever was obtained in all patients, in 2 to 3 days after treatment. However, three patients relapsed after 2 weeks and required an additional course of immune globulin.

Support for using immune globulin to treat cytomegalovirus infection and as prophylaxis against cytomegalovirus infection can be found in two meta-analyses conducted by Glowaki (1994) and Ratko (1995). The use of intravenous immune globulin (IVIG) as passive immunization for the prevention of symptomatic cytomegalovirus disease in the transplant population.

Support for using immune globulin as desensitization therapy in patients undergoing a heart transplant can be found in guidelines published by the Canadian Cardiovascular Society/Canadian Cardiac Transplant Network. Immune globulin, targeted B cell (rituximab), and plasma cell therapies (bortezomib) form the foundation of desensitization treatments. Immunoglobulin and rituximab have increased transplantation rates, reduced wait list time, and reported graft outcomes similar to those of non-sensitized patients. However, there are no randomized trials on efficacy of desensitization therapy in heart transplant.

Support for using immune globulin to treat dermatomyositis can be found in a guideline published by the European Dermatology Forum/European Academy of Dermatology and Venereology. High dose IVIG is indicated in all severe forms of dermatomyositis. Immune globulin should generally be used as adjunctive therapy.

Support for using immune globulin to treat diabetic amyotrophy can be found in a case report by Ogawa et al. Treatment with immune globulin (IVIG) restored the ability to walk in a 49-year-old woman with diabetic amyotrophy (DA) of the thighs. The woman did not receive antidiabetic treatment for 14 years after diagnosis

of diabetes mellitus. Three years after starting treatment, she began hemodialysis because of the diabetic nephropathy. A year later she began noticing weakness and atrophy of both thighs, though without pain or sensory disturbance, and she began to walk with a cane. In a short time, she became confined to a wheelchair and was diagnosed with DA. Treatment with an aldose reductase inhibitor and vitamin B12 were ineffective. She was given a 3-day course of IVIG 400 mg/kg/day (a reduced dose because of concern for congestive heart failure). On the following day, she could walk with a cane. Four weeks later she was given a second course of IVIG. Three days later she could walk unassisted. Follow-up needle electromyography suggested inactivation of proximal neuropathy. The patient experienced no adverse effects.

Support for using immune globulin to treat Hopkin's syndrome can be found in a case report published by Cohen et al (1998). A 15-year-old child experienced near complete recovery of muscle paralysis and atrophy after treatment with IV gamma globulin. Patient was diagnosed with poliomyelitis-like syndrome after an asthmatic attack. Moderate improvement in muscle strength was seen 3 weeks after patient received IV gamma globulin 1 g/kg/day for 2 consecutive days. A second treatment course was given 3 weeks later. Two years later this patient reported minimal weakness of the left deltoid muscle and he is able to play basketball.

Support for using immune globulin to treat acute disseminated encephalomyelitis (ADEM) can be found in a case series by Nishikawa et al (1999). Intravenous immune globulin (IVIG) 400 mg/kg/day for 5 consecutive days was effective in the treatment of 3 pediatric cases (ages 2 to 5 years) of ADEM. Signs and symptoms included fever, headache, vomiting and somnolence with elevated myelin basic protein in the cerebrospinal fluid (CSF) and increased signal intensity (white matter lesions) on T2-weighted magnetic resonance imaging. Each patient recovered fully within 1 to 3 weeks of IVIG therapy. Although corticosteroids have been the drug of choice for ADEM, they should be avoided in viral encephalitis. Therefore, the authors recommend IVIG therapy for suspected ADEM, reserving steroids for those who fail IVIG.

Support for using immune globulin as prophylaxis against enteritis due to rotavirus can be found in a study by Barnes et al. During the first week of life, 75 low-birth-weight neonates received oral human IgG or placebo with each feeding. IgG or placebo was given in doses of 4 mL 4 times daily during the first 7 days of life starting with the first feeding following birth. Each 4 mL of IgG contained approximately 500 mg of IgG. Twenty-five of 75 babies excreted rotavirus during the first 2 weeks of life. In babies with rotavirus, IgG was associated with delayed excretion of rotavirus and with milder symptoms of the infection. Six of 11 babies given placebo and 1 of 14 babies given IgG required low lactose feeds to alleviate rotavirus associated diarrhea. Oral human IgG protects low-birth-weight infants from diarrhea caused by rotavirus, especially in infants unprotected by other means (i.e., breastfeeding, rooming in).

Support for using immune globulin to treat epilepsy can be found in a study by Ariizumi et al. High doses of an immune globulin preparation (97% IgG and 3% IgA) were effective in producing complete clinical and electroencephalogram remission in 4 of 8 children with intractable epilepsy with attacks for 2 years or less. The probability of a successful response appeared to correspond to a short duration of illness and low serum IgA level.

Support for using immune globulin to treat gastroenteritis can be found in a study by Guarino et al. A prospective, double-blind placebo-controlled trial was conducted in 98 children with gastroenteritis (mean age 15 months +/- 8 months). Children randomized to receive a single oral dose of intravenous immune globulin (IVIG) 300 mg/kg had significantly faster improvement in stool pattern and clinical symptomatology than those receiving placebo (duration of diarrhea was 76 vs 131 hours in the placebo groups; hospital stay was 4 days in the IVIG group and 6 days in the placebo group.

Support for using immune globulin to treat granulomatosis with polyangiitis can be found in a guideline published by Groh et al. IVIG can be considered as second-line therapy for patients on glucocorticoids with or without other immunosuppressants with EGPA flares refractory to other treatments or during pregnancy. In the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections, immune globulin replacement may be considered.

Support for using immune globulin to treat Guillain-Barre syndrome can be found in two published studies. Intravenous immune globulin (IVIG) was at least as effective as plasma exchange (PE) in altering the course of Guillain-Barré syndrome (GBS) (van der Meche, 1994). One hundred forty-seven patients who were unable to walk 10 meters independently, were randomized to receive either PE (200 mL/kg in 5 sessions) over 7 to 14 days or IVIG (0.4 g/kg/day) for 5 days. In 12 patients, 1 session or more of PE had to be discontinued due to hypotension and problems with venous flow; 1 patient required discontinuation due to transient elevation of

liver enzymes. In the PE group 34% of patients improved 1 functional grade or more after 4 weeks, compared with 53% in the IVIG group. This was a statistically significant difference. The median time to improvement of at least one grade was quicker in the IVIG group (27 days) when compared to the PE group (41 days). This was also a statistically significant difference. Sixty-eight complications occurred in the PE group and 39 in the IVIG group (eg, 27% of the IVIG patients required artificial ventilation in the second week vs 42% of the PE group. The investigators conclude that IVIG is at least as effective as PE.
Intravenous immune globulin (IVIG) therapy produced similar results as plasma exchange (PE) in a multicenter, randomized, controlled trial of 225 patients with Guillain-Barré syndrome conducted by the Plasma/Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. When IVIG was combined with PE therapy, results were similar compared to PE or IVIG therapy alone. All patients, regardless of the treatment regimen received, exhibited similar ability to walk unaided, median times to hospital discharge and return to work, and ability to walk at 48 weeks after therapy. Patients in the study who had a longer delay from onset to randomization had significantly more improvement after 4 weeks than those with short delays (p less than 0.001). Patients received 5 or 6 PEs of 50 mL/kg; IVIG (Sandoglobulin(R)) was dosed at 0.4 g/kg/day for 5 days.

Support for using immune globulin as prophylaxis against hemolytic disease of fetus or newborn due to RhD isoimmunization can be found in a study by de la Camara et al. IV immune globulin was effective as prenatal therapy following severe Rh immunization, improving the outcome of pregnancy, in two patients.

Support for using immune globulin to treat hemophagocytic syndrome can be found in a study by Freeman et al. Three pediatric patients with hemophagocytic syndrome were successfully treated with intravenous immune globulin (IVIG) 1 g/kg followed by packed RBCs. All patients had significant increases in their RBC counts and decreasing tissue enzyme values soon after infusion. While some investigators caution that IVIG should not be considered sole therapy for hemophagocytic syndrome, successful treatment of a 4 1/2-year-old patient with IVIG has also been reported.

Support for using immune globulin to induce factor VIII immune intolerance can be found in a study by Nilsson et al. Successful induction of immune tolerance was achieved with a combination of factor VIII, cyclophosphamide, and high-dose IV immune globulin, in patients with hemophilia A who had developed antibodies to factor VIII. Cyclophosphamide was given from day 1 of treatment in doses of 12 to 15 mg/kg/day IV for 2 days (first dose given immediately prior to infusion of factor A), followed by oral administration of 2 to 3 mg/kg/day for 8 to 10 days. Factor VIII was given initially in doses sufficient to neutralize the inhibitor and then to raise factor VIII coagulant activity to a concentration of 40 to 100 international units/dL; factor VIII was then administered in intervals of 8 to 12 hours to maintain factor VIII coagulant activity at a level of 30 to 80 international units/dL. When decreases in factor VIII coagulant activity were observed, the daily dose of factor VIII was increased by administration of highly purified commercial virus-inactivated factor VIII concentrates at shorter intervals. Immune globulin was given initially in doses of 2.5 to 5 g IV, immediately after the first loading dose of factor VIII; beginning on day 4 of treatment, immune globulin was administered in doses of 0.4 g/kg/day for 5 days. In addition, when concentrations of factor VIII inhibitors were high initially (greater than 3 Malmo inhibitor units/mL), the antibodies were first removed by extracorporeal adsorption to protein A. With this regimen, factor VIII coagulant antibodies disappeared in 9 of 11 patients with hemophilia A following 2 to 3 weeks of combined therapy, with the half-life of infused factor VIII normalizing in 8 of these 9 patients. Stabilization of the tolerant state was observed for a median of 30 months. These data suggest that the combination of all 3 components (cyclophosphamide, factor VIII and immune globulin) are required to achieve successful induction of tolerance to factor VIII. Prior therapy in the above patients with factor VIII and cyclophosphamide and with factor VIII and immune globulin had been ineffective.

Support for using immune globulin to treat moderate and severe immune checkpoint inhibitor-related toxicities can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-Related Toxicities. The NCCN Guideline supports the use of immune globulin for the management of the below toxicities:

1. As a further intervention for myocarditis if no improvement within 24-48 hours of starting high-dose methylprednisolone
2. As an adjunct to rituximab for severe (G3) or life-threatening (G4) bullous dermatitis
3. For Stevens-Johnson syndrome, or toxic epidermal necrolysis
4. For moderate, severe, or life-threatening steroid-refractory myositis (proximal muscle weakness, neck flexor weakness, with or without myalgias) for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids
5. As treatment for severe (G3-4) myasthenia gravis

6. As treatment for moderate (G2) or severe (G3-4) Guillain-Barré Syndrome or severe (G3-4) peripheral neuropathy in combination with high-dose methylprednisolone
7. As treatment for encephalitis in combination with high-dose methylprednisolone if severe or progressing symptoms (strongly consider if progressing over 24 hours)
8. For demyelinating disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis)
9. For moderate (G3) pneumonitis if no improvement after 48-72 hours of corticosteroids or severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone

Support for using immune globulin to treat hypogammaglobulinemia from CAR-T therapy can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-Related Toxicities. The NCCN Guideline supports the use of immune globulin for the management of the below toxicities:

1. For the management of G4 cytokine release syndrome* that is refractory to high-dose corticosteroids and anti-IL-6 therapy
2. After anti-CD19 CAR T-cell therapy as replacement for hypogammaglobulinemia in select patients (those with serum IgG levels <400-600 mg/dL and serious or recurrent infections [particularly bacterial]) until serum IgG levels normalize and infections resolve

Support for using immune globulin to treat herpes gestationis can be found in a study by Harman and Black. When administered as two courses over 5 weeks, intravenous immune globulin (IVIG) 400 mg/kg/day for 5 consecutive days induced a short-term remission and decreased the autoantibody titer in a 17-year-old female who was 6 months postpartum. Intolerant to corticosteroids, the patient required cyclosporine for long-term maintenance.

Support for using immune globulin to prevent bacterial infections in HIV-infected patients can be found a report from the American Academy of Pediatrics. Intravenous immune globulin may be used for prevention of serious bacterial infections in HIV-infected pediatric patients with hypogammaglobulinemia. Use may also be considered in HIV-infected pediatric patients experiencing recurrent, serious bacterial infections (meningitis, bacteremia, pneumonia) over a 1-year period. However, in children receiving trimethoprim-sulfamethoxazole for Pneumocystis jiroveci infection (PCP) prophylaxis, IV immune globulin may not provide any additional benefit.

Support for using immune globulin to prevent bacterial infections in post-surgical or ICU patients can be found in a several studies. Siber et al conducted a double-blind, randomized, 3-arm study involving 329 ICU patients (Anon, 1992) to assess the prophylactic efficacy of hyperimmune anti-lipopolysaccharide intravenous immune globulin (IVIG) (400 mg/kg every week) or standard IVIG (400 mg/kg every week) to placebo. The adult patients were stratified by surgery type and were randomized to 1 of the 3 treatment groups. The number of patients in whom late onset infections developed was significantly lower in the standard IVIG group than in placebo (30 of 109 vs 53 of 112 patients, respectively), as was the incidence of pneumonia (15 vs 30). The number of days spent in ICU was also lower in the standard IVIG group. In contrast, the hyperimmune IVIG preparation had no detectable, prophylactic effect on infection. Investigators have commented that the inconsistent benefit of IVIG to prevent nosocomial infections is due to variable levels of antibodies in standard preparations.
Pilz and colleagues found early intravenous immune globulin (IVIG) treatment improves disease severity and may improve prognosis in prospectively score-identified high-risk postcardiac surgical patients. Patients (n=1341) at risk for sepsis after cardiac surgery were compared to 881 matched historical control patients. Patients were stratified according to risk for sepsis using a proven scoring system, APACHE (the Acute Physiology and Chronic Health Evaluation). They were treated with IVIG (Psomaglobin N: day 1 (8 mL/kg), day 2 (4 mL/kg); or Pentaglobin: days 1, 2, and 3 (5 mL/kg). Following IVIG administration, prompt and marked improvements in disease severity (i.e., a fall in APACHE score) were reported. Significantly higher score response rates, and a reduction in mortality as compared to control groups was noted, especially in the high-risk group. For the high-risk group receiving IVIG, the mean survival time of the nonsurvivors was 18.3 days as opposed to 8.3 days in the matched control group.

Support for using immune globulin to treat Isaacs syndrome can be found in a study by Ishii et al. Intravenous immune globulin (200 mg/kg/day; total 50 g) was found to worsen the symptoms of Isaac syndrome while an initial and repeat plasma exchange in a 41-year-old patient allowed symptoms to disappear for 2 to 3 weeks.

Support for using immune globulin to treat Japanese encephalitis virus disease can be found in a study by Caramello et al. In a case report, a 49-year-old man recovered from Japanese encephalitis (JE) following a 5-

day course of intravenous immune globulin (IVIG). The patient was stuporose, somnolent, disoriented, febrile and had mild meningismus, photophobia and mild conjunctival hyperemia symptoms following a 3-week trip to rural Vietnam. Serologic tests via immunofluorescence were positive for JE. Saline and noncorticosteroid antiinflammatory therapy did not improve the patient's worsening confusion and agitation. On day 6 of hospitalization, a 5-day course of IVIG was initiated at 400 mg/kg, which generated symptom improvement after the first infusion. On day 23, the patient was discharged with no residual lesions and an EEG showed regression of theta-delta waves. One month later during follow-up, there was only a slight deficit in recent memory.

Support for using immune globulin to treat severe IgA nephropathy can be found in a study by Rostoker et al. A small, open prospective cohort study involving 11 patients with severe IgA nephropathy (9 with idiopathic disease and 2 with Henoch-Schonlein purpura) found a substantial decrease in proteinuria (5.2 g/day vs 2.25 g/day), hematuria and leukocyturia after intervention with IV immune globulin (2 g/kg/month x 3 months) and IM immune globulin (0.35 mL of 16.5%/kg every 15 days x 6 months). The decrease in GFR slowed or stopped and the staining intensity of glomerular IgA and C3 deposits also decreased.

Support for using immune globulin to treat lysinuric protein intolerance can be found in a case study by Dionisi-Vici et al. A 10-year-old boy with lysinuric protein intolerance, an autosomal recessive disease of defective intracellular protein transport, recovered after a single IV immune globulin dose of 1 g/kg. No relapses occurred over 2 years of follow-up.

Intravenous immunoglobulin (IVIG) has been shown to be ineffective for the prophylaxis of, and as a treatment adjunct in, infections in some high-risk, preterm, low-birth-weight neonates (USPDI, 2002). Studies published before 1990 suggested that prophylactic IVIG reduced nosocomial infections in low-birth-weight infants. However, these studies enrolled small numbers of patients; employed varied designs, preparations, and doses; and included diverse study populations. The National Institute of Child Health and Human Development (NICHHD) Neonatal Research Network therefore performed a prospective, multi-center, randomized trial to test the hypothesis that the intravenous administration of immune globulin to infants with birth weights between 501 and 1,500 grams would reduce the incidence of nosocomial infections (Fanaroff et al, 1994). In this trial, the repeated prophylactic administration of IVIG failed to reduce the incidence of nosocomial infections significantly in premature infants weighing 501 to 1,500 grams at birth. Furthermore, there were no significant differences in morbidity, mortality, or the duration of hospitalization between infants given IVIG and infants given no infusion or an infusion and placebo.

Support for using immune globulin to treat neonatal jaundice can be found in a study by Tanyer et al. Infants with isoimmune hemolytic jaundice who received multiple doses of intravenous immune globulin (IVIG) required less phototherapy than similar infants receiving a single dose or no IVIG. Sixty-one full-term babies with blood group incompatibility received multiple doses of IVIG 500 mg/kg, a single dose, or no IVIG, within 2 to 4 hours after admission for neonatal jaundice. All infants received phototherapy. Phototherapy was stopped when the bilirubin had decreased to a safe limit. In the multiple-dose group, there was no need for exchange transfusion (multiple dose vs single dose, p less than 0.05). Twelve percent of the babies in the single-dose group and 33% in the group without IVIG required exchange transfusions (p less than 0.05 and p less than 0.01, respectively compared to the multiple dose group). The duration of phototherapy was significantly less for the treated groups than for the untreated group (p less than 0.05).

Support for using immune globulin to treat otitis media can be found in a study by Ishikaza et al. Mean pneumococcal IgG and IgG2 antibody levels were significantly lower in 7 patients with recurrent acute otitis media as compared to healthy controls. They further found that following treatment with IV immune globulin (200 mg/kg every 4 weeks for 6 months), the antibody levels increased, and episodes of infection decreased. Gray conducted a 5-year, double-blind, multicenter trial. Hyperimmune bacterial polysaccharide immune globulin (BPIG) demonstrated some efficacy in children (less than 24 months) with 1 to 3 prior episodes of acute otitis media. The 76 children were randomized to receive either BPIG (0.5 mL/kg) or saline IM at entry into the study and 30 days later. During the 120-day follow-up period, the incidence of acute otitis media infections, documented by aspiration and culture of middle ear fluid, were similar in the BPIG and placebo groups. As expected, pneumococcal acute otitis media was significantly less frequent in the BPIG recipients (0.21 vs 0.45 episode/patient), and the time spent free of acute otitis media was longer in BPIG patients (51 vs 35 days). This study demonstrated that circulating antibody, even without stimulation of specific local immunity, may prevent infection of the middle ear.

Support for using immune globulin to treat paraneoplastic visual loss can be found in a study by Guy and Aptsiauri. In 2 out of 3 cases, patients with paraneoplastic visual loss benefited from intravenous immune globulin (IVIG) therapy. Marked improvement in visual acuity and visual field reported in a 62-year-old woman diagnosed with metastatic adenocarcinoma after treatment with IVIG therapy for a total dose of 2 g/kg over 5 days. Mixed results are seen in the following two cases: a 77-year-old woman presented with loss of vision on her left eye. She received IVIG 400 mg/kg over 5 days resulting in no change in light perception. A search for an occult malignant neoplasm revealed uterine cancer. A 71-year-old man diagnosed with adenocarcinoma of the pancreas with progressive loss of vision in his right eye received a dose of IVIG 400 mg/kg. He reported an improvement in the visual field defect in the right eye, with no change in visual acuity. Patient declined further treatment due to shortness of breath and itching.

Support for using immune globulin to treat polyarteritis nodosa can be found in a case report by Viguier, Guillevin and Laroche. Immune globulin therapy brought complete regression of parvovirus B19-associated polyarteritis nodosa in a 33-year-old woman. The women presented with asthenia, fever, palpable purpura, intense myalgia, paresthesias, and polyarthritis of the hand joints. Biopsies showed small- and medium-vessel vasculitis. Parvovirus B19-specific IgM and IgG antibodies and parvovirus DNA were found in serum. The patient was given IV immune globulin 1 g/kg/day for 2 days. Her condition had improved dramatically within a week, and a month later she was in complete clinical remission, although parvovirus B19 DNA was still detectable in her serum. Three years later she remained well.

Support for using immune globulin to treat polymyositis can be found in the guidelines published by European Federation of Neurological Societies (EFNS). As second-line treatment, IVIG can be considered as a treatment option in polymyositis.

Support for using immune globulin to treat post-transplant lymphoproliferative disorder can be found in a study by Cantarovich et al. Two patients recovered from post-transplantation lymphoproliferative disorder (PTLD) after receiving a combination of intravenous immune globulin (IVIG) and interferon alpha-2b. A 60-year-old female initially developed this complication 2 months after cardiac transplant. The manifestations of PTLD over the next 5 months included liver, spleen, lung and nasopharyngeal nodules. A 65-year-old male experienced onset of PTLD 8 months after liver transplant, including subQ and liver nodules. Both patients received the combination of IVIG (0.5 g/kg every 15 days) and interferon-alpha-2b (2 million units subcutaneously 3 times/week) for a total of 4 to 12 months. Their times to complete recovery from PTLD were 3 and 7 months, respectively. Corresponding lengths of remission were 47 and 33 months, respectively.

Support for using immune globulin to treat pure red cell aplasia can be found in a study by McGuire et al. Intravenous immune globulin was used to treat a 12-month-old girl with antibody-medicated pure red cell aplasia. The response was gradual with a rise in reticulocyte count from 0.1% to 3.8% at 3 weeks and a peak count of 10.5% five weeks after initiation of therapy.

Support for using immune globulin to treat pyoderma gangrenosum can be found in a study published by Herberger and colleagues. The authors observed that corticosteroids and cyclosporine A are frequently ineffective as 1st-line therapies in the treatment of pyoderma gangrenosum (PG) and associated with a number of AEs. In a retrospective, dual-center, cohort study, these investigators examined the safety and effectiveness of biologics and IVIGs in the treatment of PG. A total of 52 patients (mean age of 58.4 years) with 75 wound episodes (mean wound size of 53.2 cm^2) were included in the study. Overall, 92.3 % of patients initially received corticosteroids (CSs; 48/52); 51.9 % cyclosporine A (CSA; 27/52). In 275 therapeutic attempts, complete remission or improvement were achieved in 63.6 % (21/33) of patients on infliximab; 57.1 % (16/28) on adalimumab; 71.4 % (5/7) on etanercept; 66.6 % (6/9) on ustekinumab, and 66.7 % (10/15) of patients who were given IVIGs. That figure was 48.8 % (38/78) for those treated with CSs and 20.0 % (7/35) for individuals on CSA. On average, AEs occurred in 18.5 % (15/81) of cases treated with biologics in 20 % (3/15) of patients receiving IVIGs, in 40 % (14/35) of individuals on CSA and in 10.4 % of those treated with CSs (5/48). The authors concluded that the present retrospective analysis suggested that both biologics (especially TNF-alpha antagonists) and IVIGs are well-tolerated and safe options in the treatment of PG. Moreover, these researchers stated that data from prospective comparative studies are highly desirable.

Support for using immune globulin to treat renal transplant rejection can be found in studies that investigated IVIG as an adjunct to plasmapheresis and IVIG alone. Lerich et al conducted a single-center, retrospective analysis of all kidney and kidney-pancreas transplant recipients (n=519) that found the 2-year graft survival was 78% in 23 patients who experienced acute humoral rejection (AHR) and treated with intravenous immune

globulin (IVIG) and plasmapheresis (PP) compared with 94% in 415 patients who experienced no rejection. The review identified 23 patients (mean age, 45 years) who experienced AHR (median time to AHR, 6 days; range, 5 to 8 days) that was confirmed by biopsy (C4d positive) and/or serological evidence (donor-specific anti-human leukocyte antigen antibodies). Twenty-two of these 23 patients were treated with IVIG and PP; one patient received PP alone. Other concomitant treatments were pulse methylprednisolone (n=13) and Thymoglobulin or OKT3 (n=7). The dose of IVIG widely varied but was usually 2 g/kg administered after the last PP session. The PP session varied based on urine output and serum creatinine, with most patients receiving 4 (range, 3 to 6 days) daily sessions. Posttransplant maintenance immunosuppression drugs were tacrolimus or cyclosporine, in combination with mycophenolate and prednisone. The median time to rejection was 6 days (range, 3 to 14 days, except for 2 patients with AHR at days 147 and 843, respectively). Renal function improved in 20 of 23 patients after treatment. Hemodialysis was required in 2 of the remaining 3 patients and transplant nephrectomy was subsequently performed in 2 of the 3 patients who failed to respond to treatment. The 2-year graft survival rates were 78% and 94% (p=0.0002) for the AHR and no rejection groups, respectively; the corresponding 2-year patient survival rates were 95% and 98% (p=0.09), respectively. The final mean serum creatinine levels were 1.8 mg/dL (interquartile range (IQR), 1.4 to 2.6 mg/dL) and 1.6 mg/dL (IQR, 1.3 to 1.8 mg/dL) in patients with functioning grafts for the AHR and no rejection groups, respectively. No adverse reactions were reported.
Luke et al conducted a retrospective review of 17 patients who manifested steroid-resistant or anti-lymphocyte antibody-resistant rejection of renal transplants. IVIG 2 g/kg was administered over 2 to 10 days during each treatment course, according to fluid balance status of each patient. Four patients required 2 courses of IVIG, and 3 had 3 or more courses. IVIG , mycophenolate mofetil, and/or steroid cycle were administered in 10 patients and IVIG alone was administered to 7 patients. After a mean of 21 months after initiating IVIG , the patient survival rate was 95% and the graft survival rate was 71%. Nine of the 17 patients showed complete resolution of rejection and 5 showed reduced severity of rejection. Among the 4 patients with anti-lymphocyte antibody- resistant rejection, IVIG completely reversed rejection in 1 patient and reduced severity in 2 patients. Reduction or resolution of rejection was demonstrated in 6 of the 7 patients who received IVIG alone. In these 7 patients, the serum creatinine level was 2.2 +/- 0.9 mg/dL at baseline, 3.7 +/- 1.2 mg/dL during rejection, and 2.7 +/- 1.3 mg/dL 2 weeks after IVIG therapy.

Support for using immune globulin to treat respiratory syncytial virus infection can be found in a study by Groothuis et al. The authors conducted a multicenter, blinded, and randomized study of respiratory syncytial virus-enriched IVIG (RSVIG) in 249 infants and children. The patients were born prematurely and were less than 6 months of age at the start of the 3-year study, had bronchopulmonary dysplasia, or congenital heart disease. During the RSV season, one group received 750 mg/kg/month, a second group received 150 mg/kg/month, and the third group received no therapy. The high-dose group had significantly fewer instances of moderate to severe RSV lower respiratory tract infections (72% less), fewer hospitalizations (63% less), fewer hospital days (63% less), fewer ICU days (97% less), and less ribavirin use than did the group receiving low-dose RSVIG or no therapy. Six deaths occurred, 3 in the low- and 3 in the high-dose group. No death, however, was attributable to RSVIG or to RSV illness.

Support for using immune globulin to treat sepsis can be found in a meta-analysis by Turgeon et al. The authors conducted meta-analysis of randomized, controlled trials comparing intravenous immune globulin (IVIG) to either placebo or no intervention. IVIG significantly decreased mortality in critically ill adults with sepsis (n=2621). Based upon a pooled analysis of 20 systematically selected trials of IVIG verses either placebo or no intervention, IVIG significantly reduced mortality of adults with sepsis, severe sepsis, or septic shock (risk ratio (RR) 0.74, 95% CI, 0.62 to 0.89; p=0.001). Similar results were found in subanalysis of the peer-reviewed, published trials and the blinded trials. Sensitivity analysis revealed severity of sepsis, IVIG dose, and duration of therapy as sources of heterogeneity. Studies evaluating severely ill adults, with a diagnosis of severe sepsis or septic shock, achieved significantly greater mortality benefit from IVIG use (RR 0.64, CI, 0.52 to 0.79; p less than 0.001) versus either placebo or no intervention, whereas studies evaluating less severely ill subjects, with a diagnosis of sepsis, did not show a mortality benefit (RR 0.89, CI, 0.71 to 1.10; p=0.25). Doses of IVIG 1 g or more per kilogram showed a significant mortality benefit versus doses less than 1 g per kilogram (RR 0.61, CI, 0.4 to 0.94; p=0.02 and RR 0.79, CI, 0.64 to 0.97; p=0.08, respectively). Duration of IVIG therapy longer than 2 days significantly reduced mortality risk (RR 0.66, CI, 0.53 to 0.82; p less than 0.002); however, IVIG therapy duration of 2 days or less showed no survival benefit over either placebo or no intervention (RR 0.98, CI, 0.74 to 1.29; p=0.86). No difference was detected between the IVIG group and the placebo or no intervention group for the secondary endpoints of length of stay in the intensive care unit or duration of mechanical ventilation.
A recent guideline published by the Surviving Sepsis campaign states IV immunoglobulins are not suggested for patients with sepsis or septic shock (weak recommendation; low quality of evidence).

Support for using immune globulin to treat Stevens-Johnson syndrome and toxic epidermal necrolysis can be found in the European guidelines on the use of high-dose intravenous immunoglobulin in dermatology (Enk et al). High-dose IVIG can be considered for confirmed Stevens-Johnson syndrome and toxic epidermal necrolysis. IVIG should be given as soon as SJS/TEN is diagnosed. In contrast, the British Guidelines for the management of SJS/TEN indicates there is insufficient evidence to support or refute benefit of IVIG in this scenario (McPherson et al).

Support for using immune globulin to treat Stiff-person syndrome can be found in a study by Dalakas. Intravenous immune globulin (IVIG) reduced stiffness parameters and factors of heightened sensitivity in patients (N=16) with stiff-person syndrome unresponsive to other agents. The mean age of study participants was 47 years (9 women, 7 men). Patients were incompletely responding to therapies. At enrollment, all patients were receiving benzodiazepines, 6 were receiving baclofen, 3 gabapentin, and 1 patient was receiving valproic acid. Doses remained unchanged throughout the study. Patients were otherwise balanced with regard to disease duration, onset of symptoms, disease severity, and other associated conditions. Immune globulin 2 g/kg IV, divided in 2 daily doses, or placebo (half-normal saline) was administered every month for 3 months. After a washout period of 1 month, the patients crossed over to the alternative therapy for another 3 months. All patients were followed for at least 3 months after the infusions. The mean number of stiff areas in the placebo group remained constant during the first 4 months but then dropped significantly in the next 3 months, after cross over. The scores of the IVIG group dropped in the first 3 months, remained constant during the wash-out period and rebounded from months 5 through 8 but never reached baseline. There was a significant difference in changes in the stiff areas between the 2 groups for the direct treatment effect on the month following each infusion and the first order carry-over effect (residual effects after 3 monthly infusions). Subanalysis of each of the stiffness areas showed a significant reduction of the stiffness in the trunk, abdomen, and the face. The duration of benefit varied from 6 to 12 weeks or up to a year. Change in the scores of distribution of stiffness index (total = 6) and heightened sensitivity (total = 7) from baseline to the 2nd and 3rd month were obtained after each treatment. The net differences in the stiffness index and heightened sensitivity scores from baseline to the end of 3 months of treatment and the first or second carry-over effects were compared between the patients randomized to the 2-treatment group for each period.

Support for using immune globulin to treat systemic lupus erythematosus can be found in the EULAR guidelines (Fanouriakis et al). Immune globulin is suggested for acute treatment of systemic lupus erythematosus-associated thrombocytopenia, as well as in cases with inadequate response to high-dose glucocorticoids, or to avoid glucocorticoid-related infections.

Support for using immune globulin to treat systemic onset juvenile chronic arthritis can be found in a study by Vignes et al. An uncontrolled pilot study (n=7) reported a 71% response rate for intravenous immune globulin (IVIG) therapy of adult onset Still disease refractory to monotherapy with nonsteroidal inflammatory agents. Patients received IVIG 2 g/kg over 2 or 5 days every 4 weeks for up to 6 cycles. Two patients did not respond to IVIG but achieved remission with oral prednisone. Of 5 responders, 1 patient relapsed after 5 months. The remaining 4 patients continued in remission for 11 to 53 months without additional IVIG.

Support for using immune globulin to treat systemic vasculitis can be found in a study by Jayne et al. IV immune globulin was effective in treating systemic vasculitis in 7 patients. Immune globulin 0.4 g/kg/day for 5 days was administered. Decreases in antineutrophil cytoplasm antibodies and C-reactive protein were observed which lasted for up to 100 days. Two of these patients had their immunosuppressive therapy discontinued prior to treatment with immune globulin, 2 other patients had not been previously treated, and the remaining patients continued other therapy during the study. The effect of immune globulin was only transient in one patient.

Support for using immune globulin to treat fetal or neonatal thrombocytopenia can be found in a study by Bussel et al. Antenatal therapy with IV immune globulin (1 g/kg over 4 to 7 hours weekly), with or without dexamethasone 3 to 5 mg daily, was reported effective in increasing fetal platelet counts in severe neonatal alloimmune thrombocytopenia. In this study, 7 pregnant women were treated with immune globulin (5 also received dexamethasone). All patients had previously had infants with severe alloimmune thrombocytopenia. Periumbilical blood sampling performed in 6 fetuses demonstrated increases in platelet counts by a mean of 72.5 x 10(9)/L. Platelet counts were above 30 x 10(9)/L at birth in all 7 treated fetuses, and no cases of intracranial hemorrhage were observed; all of the 7 infants who were untreated had lower platelet counts, with 3 developing intracranial hemorrhage (antenatal in 2 infants). Mild intrauterine growth retardation was observed in 1 treated infant (whose mother received dexamethasone concurrently), and oligohydramnios

occurred in 4 dexamethasone-treated patients during the third trimester. However, all 7 infants developed normally during follow-up of 2 months to 4 years following birth. Percutaneous umbilical blood sampling should be performed at 20 to 22 weeks gestation in women who have previously delivered an infant with alloimmune thrombocytopenia and a platelet count under 30 x 10(9)/L at birth; IV immune globulin therapy is recommended weekly if the fetal platelet count drops below 100 x 10(9)/L. Sampling should be repeated 4 to 6 weeks later to evaluate effects of treatment. In the case of treatment failure, early Caesarean section is the primary alternative, although selective platelet transfusion may also have a role.

Support for using immune globulin to treat toxic necrotizing fasciitis and toxic shock syndrome can be found in a study by Darenberg et al. In a double-blind, placebo-controlled trial of 21 patients with streptococcal toxic shock syndrome caused by severe invasive group A streptococci infection, with or without necrotizing fasciitis, there was a 3.6-fold lower mortality rate at 28 days in patients receiving adjunctive therapy of intravenous immune globulin (IVIG) compared to placebo. The study randomized patients to receive either IVIG 1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3, or to the placebo group receiving 1% albumin. Adjunctive therapy consisted of clindamycin 600 mg IV 3 times daily plus benzylpenicillin 12 g/day or cefuroxime 1.5 g 3 times per day in penicillin allergic patients. The study was terminated prematurely due to slow patient recruitment. Primary endpoint analysis demonstrated the morality rate at day 28 as 1 patient in the IVIG group (n=10), and in 4 patients in the placebo group (n=11). There were no significant differences in secondary endpoint analysis: time to resolution of shock in the survivors (mean of 88 hours vs 122 hours), or mortality at day 180 (2 vs 4 patients) in the IVIG and placebo groups, respectively.

Support for using immune globulin to treat heart transplant rejection can be found in a study by Jordan et al (1998). Rapid improvement in treating antibody-mediated allograft rejection is reported within 2 to 5 days after high-dose intravenous immune globulin (IVIG) (2 g/kg) treatment in all 10 patients in the study. IVIG also contains anti-idiopathic antibodies that are potent inhibitors of donor-specific human leukocyte antigen alloantibodies, thus preventing organ rejection episodes.

Support for using immune globulin to desensitize a highly sensitized patient awaiting renal transplantation can be found in a study by Jordan et al (2004). Successive, pretransplant treatments with high-dose intravenous immunoglobulin (IVIG) in highly sensitized patients with ESRD significantly improved the transplantation rate and time to transplantation compared with placebo in the multicenter, randomized, double-blind National Institutes of Health (NIH) IG02 trial (n=98). Highly sensitized adults (panel reactive antibody (PRA), 50% or greater every month for 3 months; mean age, 40.7 years; range, 20 to 73 years; 57% female) were randomized to receive pretransplant infusions of either IVIG 2 g/kg (maximum, 180 g; Gamimune(R) N 10% SD) (n=48; prior transplant, 73%) or placebo (n=50; prior transplant, 58%) every month for 4 months. If not transplanted after 4 months, additional infusions were given at 12 and 24 months, with follow-up until 30 months. If transplanted after 4 months, patients received additional blinded infusions monthly for 4 months. The mean PRA 1 to 3 months before study entry was approximately 80% or higher. Six patients (nonadherent group) were excluded from the analysis because they either failed to initiate therapy (n=4) or received crossover therapy (n=2; assigned to placebo but received IVIG). Among the dosing-adherent group (n=92), the transplantation rate in the IVIG group (35%; 16 of 46) was twice that in the placebo group (17%; 8 of 46) (p=0.048). Among patients who had received a previous transplant, transplantation rates were 22% (10 of 34) and 7% (3 of 28) in the IVIG and placebo groups, respectively. In addition, pretreatment with IVIG significantly reduced time to transplantation compared with placebo (p=0.049), and this improvement remained significant after adjusting for receipt of previous transplantation (p=0.034). The projected mean time to transplantation (assuming constant hazard rate) was estimated to be 4.8 years for IVIG compared with 10.3 years for placebo. Pretransplant treatment with IVIG significantly reduced mean PRA levels for IgG plus IgM (p=0.033) and IgG alone (p=0.007) relative to placebo; however, the mean PRA at each time point during the study period was greater than 40%. Notably, PRA levels returned to near baseline at 6 months following IVIG infusion. Among all transplant recipients (includes 3 patients from the nonadherent group), significantly more acute rejection episodes occurred in the IVIG group (9 of 17) than the placebo group (1 of 10) (p=0.042). However, among the dosing-adherent transplant recipients, graft failure rates during the 30-month follow-up period (25% vs 38%, respectively) and 2-year graft survival rates (80% vs 75%, respectively) were similar in the IVIG and placebo groups. Overall, IVIG was well tolerated; the incidence of headache was greater with IVIG compared with placebo (52% vs 30%).

Support for using immune globulin to treat uveitis can be found in a study by LeHoang et al. Use of intravenous immune globulin (IVIG) provided a safe and effective therapy for patients with birdshot retinochoroidopathy, a bilateral autoimmune posterior uveitis. For induction therapy, patients (n=18) received IVIG 0.4 g/kg/day for 4 days every 4 weeks for 6 months. Thereafter, patients received IVIG 1.2 to 1.6 g/kg

over 2 to 4 days at 6 to 8 week intervals. Within the first 3 months, patients experienced visual field improvements and within 2 to 6 months, improvements in visual acuity and macular edema improved. After 6 months, in the 26 eyes with a visual acuity of 20/30 or less, 14 eyes improved by at least 2 lines and 2 eyes deteriorated. In 5 patients with an initial visual acuity of 20/25, visual acuity increased to 20/20 in 4 and remained unchanged in 1. In 5 eyes with an initial acuity of 20/20, 4 remained stable and 1 deteriorated. Initially macular edema was present in 23 eyes with 17 eyes showing a decrease in macular edema on fundus fluorescein angiograms after 6 months. After a mean follow-up period of 39 months, 33 out of 36 eyes continued to show improved or stable visual acuity.

Support for using immune globulin to treat von Willebrand disorder can be found in two case studies. Intravenous immune globulin (IVIG) was efficacious when administered to a 47-year-old man with acquired Von Willebrand syndrome (Hanley et al). A 5-day course of IVIG 400 mg/kg/day was administered prior to orthopedic surgery and anticoagulation treatment was continued following surgery. At 7 days following the IVIG course, there was normalization of clotting factors and von Willebrand factors/cofactors.
Sampson et al reported temporary restoration of von Willebrand factor with control of bleeding episodes in a 75-year-old man diagnosed with acquired type 2a von Willebrand disease. This patient has received repeated treatments of intravenous immune globulin (IVIG) 30 g/day for 5 days after each bleeding episode over the past 3 years.

Pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (cicatricial pemphigoid) and epidermolysis bullosa acquisita are covered according to the conditions outlined in National Coverage Determination Manual section called Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases (250.3- Version 1).

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IXEMPRA (ixabepilone)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. In combination with capecitabine for patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated
   2. As a single agent for patients with metastatic or locally advanced breast cancer after failure of an anthracycline, a taxane, and capecitabine

B. Compendial Use
   Breast cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: HER2 status testing results, where applicable

III. CRITERIA FOR INITIAL APPROVAL

Breast Cancer
Authorization of 12 months may be granted for treatment of breast cancer when any of the following criteria are met:
1. Member has human epidermal growth factor receptor 2 (HER2)-negative locally advanced, recurrent or metastatic disease or disease with no response to preoperative systemic therapy, as a single agent; or
2. Member has human epidermal growth factor receptor 2 (HER2)-positive recurrent or metastatic disease or disease with no response to preoperative systemic therapy, in combination with trastuzumab; or
3. The requested medication will be used in combination with capecitabine for treatment of metastatic or locally advanced disease when the following criteria are met:
   a. Member has failed an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated; and
   b. Member does not have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level greater than 2.5 times the upper limit of normal (ULN) or bilirubin greater than 1 time the ULN.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section III when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Ixempra.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Breast Cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ixempra are covered in addition to recurrent or metastatic breast cancer.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Ixempra to treat recurrent or metastatic breast cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Ixempra [package insert]. Princeton, NJ: R-Pharm US LLC; January 2023.
2. The NCCN Drugs & Biologics Compendium 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 2023.

IZERVAY (avancincaptad pegol)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Izervay is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Chart notes or medical records confirming the diagnosis of geographic atrophy (GA) secondary to AMD.

III. EXCLUSION

A. Coverage will not be provided beyond 12 months of therapy.
B. Coverage will not be provided for the treatment of geographic atrophy (GA) secondary to a condition other than AMD (such as Stargardt disease, cone rod dystrophy, toxic maculopathies).

IV. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with an ophthalmologist.

V. CRITERIA FOR INITIAL APPROVAL

Geographic atrophy (GA) secondary to age-related macular degeneration
Authorization of up to 12 months may be granted when all of the following criteria are met:
A. Member has a diagnosis of geographic atrophy secondary to age-related macular degeneration.
B. Member will receive 2 mg injection into each affected eye once monthly for up to 12 months.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Izervay.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Age-Related Macular Degeneration Preferred Practice Pattern 2019

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Izervay are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCE

1. Izervay [package insert]. Parsippany, NJ: Iveric Bio Inc; August 2023.
2. Age-Related Macular Degeneration PPP 2019. American Academy of Ophthalmology. Published October 2019. Accessed December 11, 2023. https://www.aao.org/education/preferred-practice-pattern/age-related-macular-degeneration-ppp

JELMYTO (mitomycin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Jelmyto is indicated for the treatment of adult patients with low-grade upper tract urothelial cancer (LG-UTUC).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions for continuation of therapy: Urine cytology and ureteroscopy report 3 months after the initiation of therapy documenting complete response.

III. CRITERIA FOR INITIAL APPROVAL

Urothelial Cancer
Authorization of 6 doses (3 months) may be granted for the treatment of non-metastatic, low-grade, low volume (5-15mm), upper tract urothelial cancer when all of the following criteria are met:
1. The requested drug will be given via pyelocalyceal administration.
2. The requested drug will be administered once weekly for the first six weeks for initiation.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member has received the first 6 doses of initiation therapy
2. Jelmyto is being used to treat an indication enumerated in Section III
3. The member will only receive a maximum of 11 additional doses of therapy
4. The member is receiving benefit from therapy. Benefit is defined as a complete response (a complete absence of tumor lesions by urine cytology and ureteroscopy) at 3 months after the initiation of the requested drug.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Jelmyto.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Bladder cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Jelmyto are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Jelmyto to treat upper genitourinary tract tumors can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Jelmyto is recommended as primary treatment for a non-metastatic, residual, low-grade, low volume (5-15 mm), solitary tumor in the upper urinary tract for patients who are not a candidate for or not seeking nephroureterectomy as a definitive treatment.

Complete or near complete endoscopic resection or ablation is recommended prior to mitomycin ureteral gel application. Mitomycin for pyelocalyceal application may be administered via ureteral catheter or a nephrostomy tube.

VII. REFERENCES

1. Jelmyto [package insert]. Princeton, NJ: UroGen Pharma, Inc.; September 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 1, 2023.

JEMPERLI (dostarlimab-gxly)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Jemperli is indicated in combination with carboplatin and paclitaxel, followed by Jemperli as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).
2. Jemperli is indicated as a single agent for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen.
3. Jemperli is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

B. Compendial Uses
1. Breast cancer
2. Colorectal cancer
3. Esophageal and esophagogastric junction cancers
4. Gastric cancer
5. Occult primary cancer
6. Ovarian cancer
    a. Epithelial ovarian cancer
    b. Fallopian tube cancer
    c. Primary peritoneal cancer
    d. Carcinosarcoma (malignant mixed Mullerian tumors)
    e. Clear cell carcinoma of the ovary
    f. Mucinous carcinoma of the ovary
    g. Grade 1 endometrioid carcinoma
    h. Low-grade serous carcinoma/ovarian borderline epithelial tumors
7. Endometrial carcinoma
8. Small bowel adenocarcinoma
9. Ampullary adenocarcinoma
10. Hepatocellular Carcinoma
11. Biliary Tract cancers
    a. Intrahepatic cholangiocarcinoma
    b. Gallbladder cancer
    c. Extrahepatic cholangiocarcinoma
12. Pancreatic Adenocarcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all initial requests:
Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor status, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Endometrial cancer (EC)

1. Authorization of 12 months may be granted as a single agent for treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.
2. Authorization of 12 months may be granted for primary or adjuvant treatment of endometrial carcinoma in combination with carboplatin and paclitaxel (for up to 6 doses of combination therapy followed by Jemperli monotherapy) in members with stage III-IV or recurrent disease.

B. Solid tumors

Authorization of 12 months may be granted as a single agent for treatment of mismatch repair deficient (dMMR) solid tumors in members with recurrent or advanced disease that have progressed on or following prior treatment and for whom there are no satisfactory alternative treatment options.

C. Breast cancer

Authorization of 12 months may be granted as a single agent in members with no response to preoperative systemic therapy, recurrent unresectable or stage IV breast cancer that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and has progressed on or following prior treatment and has no satisfactory alternative treatment options.

D. Colorectal cancer

Authorization of 12 months may be granted as a single agent for subsequent treatment of advanced or metastatic colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), following previous oxaliplatin-irinotecan- and/or fluoropyrimidine-based therapy, if no previous treatment with a checkpoint inhibitor.

E. Esophageal, esophagogastric junction and gastric cancer

1. Authorization of 12 months may be granted for treatment of esophageal cancer, esophagogastric junction cancer, or gastric adenocarcinoma when all of the following criteria are met:
   a. The requested medication will be used as a single agent.
   b. The requested medication will be used as palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease.
   c. The requested medication will be used for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors.
   d. The requested medication will be used in patients whose cancer is progressing on or following prior treatment and who have no satisfactory alternative treatment options.
   e. The member has not received prior use of immuno-oncology therapy.
2. Authorization of 12 months may be granted for treatment of gastric adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) in members who are medically fit for surgery with surgically unresectable locoregional disease.

F. Occult primary cancer

Authorization of 12 months may be granted as a single agent for treatment of occult primary cancer that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and has progressed on or following prior treatment and has no satisfactory alternative treatment options.

G. Ovarian cancer

Authorization of 12 months may be granted as a single agent for treatment of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, carcinosarcoma (malignant mixed Mullerian tumors), clear cell carcinoma of the ovary, mucinous carcinoma of the ovary, grade 1 endometrioid carcinoma, and low-grade serous carcinoma/ovarian borderline epithelial tumors for recurrent, persistent, or advanced microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.

H. Small bowel adenocarcinoma

Authorization of 12 months may be granted as a single agent for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors if no previous treatment with a checkpoint inhibitor.

I. Ampullary adenocarcinoma

Authorization of 12 months may be granted as a single agent for subsequent treatment of recurrent or advanced microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma that has progressed on or following prior treatment and has no satisfactory alternative treatment options.

J. Biliary Tract cancers

Authorization of 12 months may be granted as a single agent for subsequent treatment of unresectable, resected gross residual (R2) disease, or metastatic gallbladder cancer, intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma that is microsatellite instability-high (MSI-H) and/or mismatch repair deficient (dMMR), if no previous treatment with a checkpoint inhibitor and no satisfactory alternative treatment options.

K. Hepatocellular Carcinoma

Authorization of 12 months may be granted as a single agent for subsequent treatment of hepatocellular carcinoma that is microsatellite instability-high (MSI-H) and/or mismatch repair deficient (dMMR), if no previous treatment with a checkpoint inhibitor and no satisfactory alternative treatment options.

L. Pancreatic Adenocarcinoma

Authorization of 12 months may be granted as a single agent for treatment of recurrent, locally advanced, metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) pancreatic adenocarcinoma.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent. Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen and
    b. No evidence of disease progression while on the current regimen

Treatment as monotherapy after combination use with carboplatin and paclitaxel for endometrial carcinoma will not be approved beyond 36 months total therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Jemperli.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Small bowel adenocarcinoma
4. NCCN Guideline: Breast cancer
5. NCCN Guideline: Hepatocellular carcinoma
6. NCCN Guideline: Occult primary
7. NCCN Guideline: Biliary tract cancers
8. NCCN Guideline: Ovarian cancer, fallopian tube cancer, and primary peritoneal cancer
9. NCCN Guideline: Uterine neoplasms
10. NCCN Guideline: Ampullary adenocarcinoma
11. NCCN Guideline: Pancreatic adenocarcinoma
12. NCCN Guideline: Colon cancer
13. NCCN Guideline: Rectal cancer
14. NCCN Guideline: Esophageal and esophagogastric junction cancers

15. NCCN Guideline: Gastric cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Jemperli are covered in addition to the following:

1. Breast cancer
2. Colorectal cancer
3. Esophageal and esophagogastric junction cancers
4. Gastric cancer
5. Occult primary cancer
6. Ovarian cancer
    a. Epithelial ovarian cancer
    b. Fallopian tube cancer
    c. Primary peritoneal cancer
    d. Carcinosarcoma (malignant mixed Mullerian tumors)
    e. Clear cell carcinoma of the ovary
    f. Mucinous carcinoma of the ovary
    g. Grade 1 endometrioid carcinoma
    h. Low-grade serous carcinoma/ovarian borderline epithelial tumors
7. Endometrial carcinoma
8. Small bowel adenocarcinoma
9. Ampullary adenocarcinoma
10. Hepatobiliary cancer
    a. Hepatocellular carcinoma
    b. Intrahepatic cholangiocarcinoma
    c. Gallbladder cancer
    d. Extrahepatic cholangiocarcinoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Jemperli to treat the compendial indications listed in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Jemperli [package insert]. Philadelphia, PA: GlaxoSmithKline; July 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed September 7, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed September 5, 2023.

JEVTANA (cabazitaxel)
cabazitaxel

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Jevtana is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.

Compendial Uses
1. Subsequent treatment for castration-resistant distant metastatic disease previously treated with a docetaxel-based regimen or in patients who are not candidates for, or are intolerant of docetaxel
2. Subsequent treatment for castration-resistant distant metastatic disease previously treated with novel hormone therapy (e.g., enzalutamide [Xtandi] or abiraterone [Zytiga])

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Metastatic castration-resistant prostate cancer (CRPC)
Authorization of 6 months may be granted for the treatment of metastatic castration-resistant prostate cancer when previously treated with any of the following:
A. A docetaxel-containing regimen or in patients who are not candidates for or who are intolerant to docetaxel
B. Novel hormone therapy (e.g., enzalutamide [Xtandi], abiraterone [Zytiga])

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Jevtana.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Prostate Cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Jevtana are covered in addition to previously treated castration-resistant metastatic prostate cancer.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Jevtana to treat previously treated castration-resistant metastatic prostate cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Jevtana [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; July 2023.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 2023.

KADCYLA (ado-trastuzumab emtansine)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Metastatic Breast Cancer (MBC)
      Kadcyla, as a single agent, is indicated for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy.

   2. Early Breast Cancer (EBC)
      Kadcyla, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

B. Compendial Uses
   1. Single-agent therapy for recurrent or stage IV (M1) HER2-positive breast cancer
   2. Non-small cell lung cancer with HER2 mutations
   3. HER2-positive recurrent, unresectable or metastatic salivary gland tumors

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: human epidermal growth factor receptor 2 (HER2) status.

III. CRITERIA FOR INITIAL APPROVAL

A. Breast cancer
   1. Authorization of 12 months may be granted for subsequent treatment of HER2-positive metastatic or recurrent breast cancer or for HER2-positive breast cancer with no response to preoperative systemic therapy when used as a single agent.
   2. Authorization of up to 12 months may be granted for adjuvant treatment of HER2-positive early breast cancer when used as a single agent.
   3. Authorization of 12 months may be granted for initial treatment of small asymptomatic brain metastases in HER2-positive breast cancer when used as a single agent.

B. Non-small cell lung cancer
Authorization of 12 months may be granted for subsequent treatment of non-small cell lung cancer with HER2 (ERBB2) positive mutations when both of the following criteria are met:
1. The disease is recurrent, advanced or metastatic
2. The requested medication will be used as a single agent

C. Salivary gland tumor

Authorization of 12 months may be granted for treatment of recurrent, unresectable or metastatic HER2-positive salivary gland tumors as a single agent.

IV. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for all members (including new members) who are continuing with the requested medication when all of the following criteria are met. Adjuvant treatment of breast cancer will be approved for a total of 12 months of therapy.

A. The member is currently receiving treatment with the requested medication.
B. The requested medication is being used to treat a diagnosis or condition enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Kadcyla.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Non-small cell lung cancer
4. NCCN Guideline: Breast cancer
5. NCCN Guideline: Central nervous system cancers
6. NCCN Guideline: Head and neck cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Kadcyla are covered in addition to the following:

1. Single-agent therapy for recurrent or stage IV (M1) HER2-positive breast cancer
2. Non-small cell lung cancer with HER2 mutations
3. HER2-positive recurrent, unresectable or metastatic salivary gland tumors

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for single-agent therapy for recurrent or stage IV (M1) HER2-positive breast cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for non-small cell lung cancer with HER2 mutations can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for HER2-positive recurrent, unresectable or metastatic salivary gland tumors can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Kadcyla [package insert]. South San Francisco, CA: Genentech, Inc.; February 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed December 1, 2023.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers. Version 4.2024. Accessed December 21, 2023. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

KALBITOR (ecallantide)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Kalbitor is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. For initial authorization:
   1. C1 inhibitor functional and antigenic protein levels
   2. F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
   3. Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
B. For continuation of therapy, chart notes demonstrating a reduction in severity and/or duration of attacks

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

IV. CRITERIA FOR INITIAL APPROVAL

Hereditary angioedema (HAE)
Authorization of 6 months may be granted for treatment of acute HAE attacks when either of the following criteria is met at the time of diagnosis:

A. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
   1. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
   2. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)
B. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
   1. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
   2. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment of acute HAE attacks when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The member is receiving benefit from therapy. Benefit is defined as a reduction in severity and/or duration of acute attacks.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Kalbitor.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.
4. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
5. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
6. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.
7. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
8. International consensus on hereditary and acquired angioedema.
9. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.
10. Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Kalbitor are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.
When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG

(plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

VIII. REFERENCES

1. Kalbitor [package insert]. Lexington, MA: Dyax Corp., a Takeda company; November 2021.
2. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010;6(1):24.
3. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy.* 2012;67:147-157.
4. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
5. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc*. 2012;33(6):S145-S156.
6. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update. *Allergy*. 2022 Jan 10. doi: 10.1111/all. 15214. Online ahead of print.
7. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109:395-402.
8. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69:602-616.
9. Bowen T. Hereditary angioedema: beyond international consensus – circa December 2010 – The Canadian Society of Allergy and Clinical Immunology Dr. David McCourtie Lecture. *Allergy Asthma Clin Immunol*. 2011;7(1):1.
10. Bernstein JA. Update on angioedema: Evaluation, diagnosis, and treatment. *Allergy and Asthma Proceedings.* 2011;32(6):408-412.
11. Longhurst H, Cicardi M. Hereditary angio-edema. *Lancet.* 2012;379:474-481.
12. Veronez CL, Csuka D, Sheik FR, et al. The expanding spectrum of mutations in hereditary angioedema. *J Allergy Clin Immunol Pract.* 2021;S2213-2198(21)00312-3.

KANUMA (sebelipase alfa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Kanuma is indicated for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests: lysosomal acid lipase enzyme assay or genetic testing results supporting diagnosis.
B. Continuation requests: lab values or chart notes documenting a positive response to therapy (e.g., improvement, stabilization, or slowing of disease progression for weight-for-age z-score if exhibiting growth failure, LDL, HDL, triglycerides, or ALT).

III. CRITERIA FOR INITIAL APPROVAL

Lysosomal acid lipase (LAL) deficiency
Authorization of 12 months may be granted for treatment of LAL deficiency when both of the following criteria are met:
A. Diagnosis of LAL deficiency was confirmed by enzyme assay demonstrating a deficiency of lysosomal acid lipase enzyme activity or by genetic testing; AND
B. Member has alanine aminotransferase level (ALT) ≥ 1.5 times the upper limit of normal (based on the age- and gender-specific normal ranges) on two consecutive ALT measurements obtained at least one week apart.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for weight-for-age z-score if exhibiting growth failure, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides, or alanine aminotransferase [ALT]).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Kanuma.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. Lysosomal Acid Lipase Deficiency (Endotext)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Kanuma are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for confirming the diagnosis with enzyme assays or genetic testing prior to using Kanuma to treat LAL deficiency can be found in an article by Wilson and Patni. LAL deficiency can be diagnosed by demonstrating deficient LAL enzyme activity, as well as by genetic testing identifying mutations of the LIPA gene. Historically, enzyme activity was measured in cultured fibroblasts, peripheral leukocytes, or liver tissue. A newer method has been developed to determine LAL activity. This method measures LAL activity in dried blood spots (DBS), and uses Lalistat 2, a highly specific inhibitor of LAL. LAL activity is determined by comparing total lipase activity to lipase activity with Lalistat 2.

VII. REFERENCES

1. Kanuma [package insert]. Cheshire, CT: Alexion Pharmaceuticals Inc.; November 2021.
2. Wilson DP, Patni N. Lysosomal Acid Lipase Deficiency. [Updated 2023 Mar 15]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395569/

KEYTRUDA (pembrolizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Melanoma
   i. Keytruda (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.
   ii. Keytruda is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma.
2. Non-Small Cell Lung Cancer
   i. Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
   ii. Keytruda, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
   iii. Keytruda, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 (Tumor Proportion Score [TPS ≥1%]) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
      a. stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
      b. metastatic.
   iv. Keytruda, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.
   v. Keytruda, in combination with platinum-containing chemotherapy, is indicated for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
   vi. Keytruda, as a single agent, is indicated for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage 1B (T2a ≥ 4cm), II, or IIIA NSCLC

3. Head and Neck Cancer Squamous Cell Cancer
   i. Keytruda, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
   ii. Keytruda, as a single agent, is indicated for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.
   iii. Keytruda, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

4. Classical Hodgkin Lymphoma
   i. Keytruda is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).
   ii. Keytruda is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more prior lines of therapy.

5. Primary Mediastinal Large B-cell Lymphoma

Keytruda is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphomas (PMBCL), or who have relapsed after 2 or more prior lines of therapy.

Limitations of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

6. Urothelial Carcinoma
   i. Keytruda, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma:
      a. who are not eligible for any platinum-containing chemotherapy, or
      b. who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
   ii. Keytruda, as a single agent, is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
   iii. Keytruda, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma.

7. Microsatellite Instability-High or Mismatch Repair Deficient Cancer
   Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

   Limitations of Use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.

8. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer
   Keytruda is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

9. Gastric Cancer

   i. Keytruda is indicated in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS≥1) as determined by an FDA-approved test.
   ii. Keytruda, in combination with fluoropyrimidine- and platinum-containing chemotherapy is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

10. Esophageal Cancer
    Keytruda is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
    i. in combination with platinum- and fluoropyrimidine-based chemotherapy, or
    ii. as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.

11. Cervical Cancer
    i. Keytruda is indicated in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
    ii. Keytruda is indicated as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumor express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

12. Hepatocellular Carcinoma
    Keytruda is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

13. Biliary Tract Cancer
    Keytruda, in combination with gemcitabine and cisplatin is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

14. Merkel Cell Carcinoma
    Keytruda is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

15. Renal Cell Carcinoma
    i. Keytruda, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
    ii. Keytruda, in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
    iii. Keytruda, for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

16. Endometrial Carcinoma
    i. Keytruda, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.
    ii. Keytruda, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

17. Tumor Mutational Burden-High Cancer
    Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

    Limitations of use: The safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.

18. Cutaneous Squamous Cell Carcinoma
    Keytruda is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

19. Triple-Negative Breast Cancer
    i. Keytruda is indicated for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery
    ii. Keytruda is indicated in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.

20. Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400mg Every 6 Weeks
    Keytruda is indicated for use at an additional recommended dosage of 400mg every 6 weeks for classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma in adults.

B. Compendial Uses
1. Non-small cell lung cancer
2. Head and neck cancer
3. Classical Hodgkin lymphoma

4. Urothelial carcinoma
5. Solid tumors
6. Anaplastic thyroid carcinoma
7. Follicular, Oncocytic (Hurthle cell), or papillary thyroid carcinoma
8. Medullary thyroid carcinoma
9. Colorectal cancer
10. Merkel cell carcinoma
11. Gastric cancer
12. Esophageal cancer and esophagogastric junction cancer
13. Cervical cancer
14. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
15. Uveal melanoma
16. Testicular cancer
17. Endometrial carcinoma
18. Anal carcinoma
19. Central Nervous System (CNS) brain metastases
20. Primary mediastinal large B-cell lymphoma
21. Pancreatic adenocarcinoma
22. Biliary Tract cancers
23. Hepatocellular carcinoma
24. Vulvar cancer
25. Thymic carcinoma
26. Mycosis Fungoides/Sezary syndrome
27. Anaplastic large cell lymphoma (ALCL)
28. Extranodal NK/T-cell lymphoma
29. Gestational trophoblastic neoplasia
31. Neuroendocrine and Adrenal Tumors
32. Prostate cancer
32. Occult primary cancer
33. Small bowel adenocarcinoma
34. Breast cancer
35. Bone cancer
36. CLL/SLL
37. Penile cancer
38. Soft tissue sarcoma
39. Uterine sarcoma
40. Ampullary Adenocarcinoma
41. Small cell lung cancer
42. Pediatric Diffuse High-Grade Gliomas
43. Kaposi Sarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Pediatric members with TMB-H central nervous system cancers.
B. Members who have experienced disease progression while on programmed death receptor-1 (PD-1) or PD-L1 inhibitor therapy (other than when used as second-line or subsequent therapy for metastatic or unresectable melanoma in combination with ipilimumab following progression on single agent anti-PD-1 immunotherapy).

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous Melanoma

Authorization of 12 months may be granted for the treatment of cutaneous melanoma in either of the following settings:
1. Treatment of unresectable, recurrent or metastatic disease.
2. Adjuvant treatment.

B. Non-small Cell Lung Cancer (NSCLC)
Authorization of 12 months may be granted for NSCLC for either of the following clinical settings:
1. Treatment of recurrent, advanced, or metastatic disease.
2. Neoadjuvant treatment when used in combination with platinum-based chemotherapy, and then continued as single agent adjuvant therapy after surgery.
3. Adjuvant treatment following resection and platinum-based chemotherapy.

C. Head and Neck Cancer
Authorization of 12 months may be granted for treatment of head and neck cancer.

D. Classical Hodgkin Lymphoma (cHL)
Authorization of 12 months may be granted for treatment of classical Hodgkin lymphoma.

E. Urothelial Carcinoma
Authorization of 12 months may be granted for treatment of urothelial carcinoma, including bladder cancer, upper genitourinary tract tumors, urothelial carcinoma of the prostate, and primary carcinoma of the urethra.

F. Solid Tumors
Authorization of 12 months may be granted for treatment of solid tumors in members with unresectable or metastatic disease that has progressed following prior treatment and have no satisfactory alternative treatment options when either of the following criteria is met:
1. The requested medication will be used for microsatellite instability-high or mismatch repair deficient solid tumors.
2. The requested medication will be used for tumor mutational burden-high (≥10 mutations/megabase) solid tumors.

G. Neuroendocrine and Adrenal Tumors
Authorization of 12 months may be granted for treatment of neuroendocrine and adrenal tumors.

H. Anaplastic Thyroid Carcinoma
Authorization of 12 months may be granted for treatment of anaplastic thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase) tumors.

I. Follicular, Oncocytic (Hurthle Cell), or Papillary Thyroid Carcinoma
Authorization of 12 months may be granted for treatment of follicular, oncocytic (Hurthle cell), or papillary thyroid carcinoma for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden-high (≥10 mutations/megabase) tumors.

J. Medullary Thyroid Carcinoma
Authorization of 12 months may be granted for treatment of medullary thyroid carcinoma for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden-high (≥10 mutations/megabase) tumors.

K. Colorectal Cancer (CRC)
Authorization of 12 months may be granted for treatment of colorectal cancer including appendiceal carcinoma when both of the following criteria are met:
1. Disease is inoperable, advanced, or metastatic.
2. Tumor is microsatellite instability-high or mismatch repair deficient.

L. Merkel Cell Carcinoma (MCC)
Authorization of 12 months may be granted for treatment of Merkel cell carcinoma.

M. Gastric Cancer
Authorization of 12 months may be granted for treatment of gastric cancer.

N. Esophageal Cancer and Esophagogastric Junction Cancer
Authorization of 12 months may be granted for treatment of esophageal cancer, including esophagogastric junction (EGJ) cancer.

O. Cervical Cancer
Authorization of 12 months may be granted for treatment of cervical cancer.

P. Epithelial Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer
Authorization of 12 months may be granted for the treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

Q. Uveal Melanoma
Authorization of 12 months may be granted for treatment of uveal melanoma.

R. Testicular Cancer
Authorization of 12 months may be granted for the treatment of testicular cancer.

S. Endometrial Carcinoma
Authorization of 12 months may be granted for the treatment of endometrial carcinoma.

T. Anal Carcinoma
Authorization of 12 months may be granted for the treatment of anal carcinoma.

U. CNS Brain Metastases
Authorization of 12 months may be granted for the treatment of CNS brain metastases in members with melanoma or non-small cell lung cancer (NSCLC).

V. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
Authorization of 12 months may be granted for the treatment of primary mediastinal large B-cell lymphoma.

W. Pancreatic Adenocarcinoma
Authorization of 12 months may be granted for the treatment of pancreatic adenocarcinoma.

X. Biliary Tract Cancers
Authorization of 12 months may be granted for the treatment of biliary tract cancers, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer.

Y. Hepatocellular Carcinoma (HCC)
Authorization of 12 months may be granted for treatment of members with hepatocellular carcinoma.

Z. Vulvar Cancer[2]
Authorization of 12 months may be granted for treatment of vulvar cancer.

AA. Renal Cell Carcinoma (RCC)
Authorization of 12 months may be granted for treatment of renal cell carcinoma.

BB. Thymic Carcinoma
Authorization of 12 months may be granted for treatment of thymic carcinoma.

CC. Mycosis Fungoides/Sezary Syndrome
Authorization of 12 months may be granted for treatment of mycosis fungoides or Sezary syndrome.

DD. Extranodal NK/T-cell lymphoma
Authorization of 12 months may be granted for treatment of extranodal NK/T-cell lymphoma.

EE. Anaplastic large cell lymphoma (ALCL)
Authorization of 12 months may be granted for treatment of anaplastic large cell lymphoma (ALCL).

FF. Gestational Trophoblastic Neoplasia

Authorization of 12 months may be granted for treatment of gestational trophoblastic neoplasia.

GG. Prostate Cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

HH. Cutaneous Squamous Cell Skin Carcinoma (cSCC)
Authorization of 12 months may be granted for treatment of cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

II. Occult Primary
Authorization of 12 months may be granted for treatment of occult primary cancer in members with microsatellite instability-high or mismatch repair deficient tumors or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase (mut/Mb) tumors).

JJ. Small Bowel Adenocarcinoma
Authorization of 12 months may be granted for treatment of small bowel adenocarcinoma, when both of the following criteria are met:
1. Disease is advanced or metastatic.
2. Tumor is microsatellite-instability high or mismatch repair deficient.

KK. Ampullary Adenocarcinoma
Authorization of 12 months may be granted as a single agent for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H ≥ 10 mut/Mb) ampullary adenocarcinoma.

LL. Breast Cancer
1. Authorization of 12 months may be granted for treatment of triple-negative breast cancer when both of the following criteria are met:
   i. The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
      a. Human epidermal growth factor receptor 2 (HER-2)
      b. Estrogen
      c. Progesterone
   ii. The requested medication will be used in combination with chemotherapy or as a single agent as adjuvant treatment after surgery.
2. Authorization of 12 months may be granted for treatment of breast cancer for recurrent unresectable or metastatic tumors or members with no response to preoperative systemic therapy when both of the following criteria are met:
   i. The disease has progressed following prior treatment and the patient has no satisfactory alternative treatment options.
   ii. The tumors are microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tissue tumor mutation burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]).

MM. Bone Cancer
Authorization of 12 months may be granted for treatment of bone cancer, including chondrosarcoma, chordoma, Ewing Sarcoma, and osteosarcoma.

NN. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Authorization of 12 months may be granted for treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma.

OO. Penile Cancer
Authorization of 12 months may be granted for treatment of penile cancer.

PP. Soft Tissue Sarcoma
Authorization of 12 months may be granted as a single agent for treatment of the following types of soft tissue sarcoma: alveolar soft part sarcoma (ASPS), myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), cutaneous angiosarcoma, and undifferentiated sarcoma.

QQ. Uterine sarcoma
Authorization of 12 months may be granted for treatment of uterine sarcoma for tumor mutational burden-high (≥10 mutations/megabase) tumors.

RR. Small Cell Lung Cancer
Authorization of 12 months may be granted for treatment of small cell lung cancer.

SS. Pediatric Diffuse High-Grade Gliomas
Authorization of 12 months may be granted for treatment of hypermutant tumor pediatric diffuse high-grade glioma.

TT. Kaposi Sarcoma
Authorization of 12 months may be granted as a single agent for subsequent treatment of relapsed/refractory endemic or classic Kaposi Sarcoma.

IV. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma, high-risk early-stage TNBC, renal cell carcinoma, or NSCLC
Authorization for 12 months total therapy may be granted for all members (including new members) who are continuing with the requested medication when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used as adjuvant treatment for any of the following indications: melanoma, high-risk early-stage TNBC, renal cell carcinoma, or NSCLC.
3. The requested medication has been effective for treating the diagnosis or condition.

B. NSCLC, head and neck cancer, cHL, PMBCL, MSI-H or dMMR Cancers, Gastric Cancer, Esophageal Cancer (including EGJ), Cervical Cancer, urothelial carcinoma, HCC, MCC, RCC, Endometrial carcinoma, cSCC, locally recurrent unresectable or metastatic TNBC, TMB-H Cancer, Biliary Tract Cancer
Authorization for 12 months (up to 24 months of continuous use) may be granted for all members (including new members) who are continuing with the requested medication when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat NSCLC, head and neck cancer, cHL, PMBCL, MSI-H or dMMR cancers, gastric cancer, esophageal cancer (including EGJ), urothelial carcinoma, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, cSCC, locally recurrent unresectable or metastatic TNBC, TMB-H cancers, and biliary tract cancers.
3. The requested medication has been effective for treating the diagnosis or condition.

C. All Other Indications
Authorization for 12 months may be granted for all members (including new members) who are continuing with the requested medication when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat any other diagnosis or condition enumerated in Section III.
3. The requested medication has been effective for treating the diagnosis or condition.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Keytruda.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
3. NCCN Guideline: Pediatric central nervous system cancers
4. NCCN Guideline: Prostate cancer

5. NCCN Guideline: Penile cancer
6. NCCN Guideline: Hodgkin lymphoma
7. NCCN Guideline: Thymomas and thymic carcinomas
8. NCCN Guideline: Small cell lung cancer
9. NCCN Guideline: Neuroendocrine and Adrenal Tumors
10. NCCN Guideline: Vulvar cancer
11. NCCN Guideline: Cervical cancer
12. NCCN Guideline: Gestational Trophoblastic Neoplasia
13. NCCN Guideline: Small bowel adenocarcinoma
14. NCCN Guideline: T-cell lymphomas
15. NCCN Guideline: Pediatric Hodgkin lymphoma
16. NCCN Guideline: Squamous cell skin cancer
17. NCCN Guideline: Cutaneous melanoma
18. NCCN Guideline: Kaposi sarcoma
19. NCCN Guideline: Pediatric aggressive mature B-cell lymphomas
20. NCCN Guideline: Bone cancer
21. NCCN Guideline: Testicular cancer
22. NCCN guideline: Merkel cell carcinoma
23. NCCN guideline: Non-small cell lung cancer
24. NCCN guideline: Breast cancer
25. NCCN guideline: Hepatocellular carcinoma
26. NCCN guideline: Soft tissue sarcoma
27. NCCN guideline: Anal carcinoma
28. NCCN guideline: Uveal melanoma
29. NCCN guideline: Gastric cancer
30. NCCN guideline: Esophageal and esophagogastric junction cancers
31. NCCN guideline: Occult primary
32. NCCN guideline: Central nervous system cancer
33. NCCN guideline: Biliary tract cancer
34. NCCN guideline: Thyroid carcinoma
35. NCCN guideline: Ampullary adenocarcinoma
36. NCCN guideline: Bladder cancer
37. NCCN guideline: Colon cancer
38. NCCN guideline: B-cell lymphomas
39. NCCN guideline: Uterine neoplasms
40. NCCN guideline: Primary cutaneous lymphomas
41. NCCN guideline: Rectal cancer
42. NCCN guideline: Chronic lymphocytic leukemia/Small lymphocytic lymphoma
43. NCCN guideline: Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
44. NCCN guideline: Pancreatic adenocarcinoma
45. NCCN guideline: Head and neck cancers
46. NCCN guideline: Kidney cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Keytruda are covered in addition to the following:

1. Non-small cell lung cancer
2. Head and neck cancer
3. Classical Hodgkin lymphoma
4. Urothelial carcinoma
5. Solid tumors
6. Adrenocortical carcinoma
7. Anaplastic thyroid carcinoma
8. Follicular, Hurthle cell, or papillary thyroid carcinoma
9. Medullary thyroid carcinoma
10. Colorectal cancer
11. Merkel cell carcinoma
12. Gastric cancer
13. Esophageal cancer and esophagogastric junction cancer
14. Cervical cancer
15. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer

16. Uveal melanoma
17. Testicular cancer
18. Endometrial carcinoma
19. Anal carcinoma
20. Central Nervous System (CNS) brain metastases
21. Primary mediastinal large B-cell lymphoma
22. Pancreatic adenocarcinoma
23. Biliary tract cancers
24. Hepatocellular carcinoma
25. Vulvar cancer
26. Thymic carcinoma
27. Mycosis Fungoides/Sezary syndrome
28. Anaplastic large cell lymphoma (ALCL)
29. Extranodal NK/T-cell lymphoma
30. Gestational trophoblastic neoplasia
31. Neuroendocrine and Adrenal Tumors
32. Prostate cancer
33. Occult primary cancer
34. Small bowel adenocarcinoma
35. Breast cancer
36. Bone cancer
37. CLL/SLL
38. Penile cancer
39. Soft tissue sarcoma
40. Uterine sarcoma
41. Ampullary Adenocarcinoma
42. Small cell lung cancer
43. Pediatric Diffuse High-Grade Gliomas
44. Kaposi Sarcoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the compendial uses in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; November2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 4, 2023.

KIMMTRAK (tebentafusp-tebn)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Kimmtrak is indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For initial requests: medical record documentation of HLA-A*02:01 phenotype.

III. CRITERIA FOR INITIAL APPROVAL

Uveal Melanoma
Authorization of 12 months may be granted for treatment of uveal melanoma when all of the following criteria are met:
A. The member is HLA-A*02:01-positive
B. The disease is unresectable or metastatic

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Kimmtrak
B. Kimmtrak is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen and
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Kimmtrak.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. NCCN Guideline: Uveal melanoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Kimmtrak are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Kimmtrak [package insert]. Conshohocken, PA: Immunocore Commercial LLC; November 2022.

KRYSTEXXA (pegloticase)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Krystexxa is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Limitations of Use
Krystexxa is not recommended for the treatment of asymptomatic hyperuricemia.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions for continuation of therapy: Documentation (e.g., chart notes, lab test results) of a response to therapy (e.g., serum uric acid levels < 6 mg/dL, reduction of tophi, reduction of symptoms and/or flares).

III. CRITERIA FOR INITIAL APPROVAL

Chronic gout
Authorization of 12 months may be granted for treatment of chronic gout when ALL of the following criteria are met:
A. The requested medication will NOT be used concomitantly with oral urate-lowering therapies.
B. The member is refractory to conventional therapy (e.g., allopurinol, febuxostat) at the maximum medically appropriate dose, or the member has a clinical reason to avoid treatment with all conventional therapies.
C. The member meets one of the following criteria:
    1. The requested medication will be co-administered with weekly oral methotrexate and folic acid or folinic acid supplementation, or
    2. The member has a contraindication to or clinical reason to avoid oral methotrexate therapy.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member has NOT had two consecutive serum uric acid levels above 6 mg/dL since starting treatment with the requested medication.
D. The member is receiving benefit from therapy (e.g., serum uric acid levels < 6 mg/dL, reduction of tophi, reduction of symptoms and/or flares).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Krystexxa.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2020 American College of Rheumatology guideline for the management of gout.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Krystexxa are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Krystexxa to treat chronic gout can be found in the most recent American College of Rheumatology guidelines for the management of gout. Krystexxa is not recommended as initial first-line urate lowering therapy (ULT) in patients with gout. Although there is moderate evidence for efficacy, there are concerns for cost and safety of pegloticase as well as favorable benefit-to-harm ratios of other first-line options. When xanthine oxidase inhibitors (XOI; i.e., allopurinol or febuxostat), uricosurics, and other interventions have failed to achieve serum urate (SU) target levels and the patient has frequent gout flares (2 or more per year) or has nonresolving subcutaneous tophi, switching to Krystexxa is recommended over continuing current ULT. However, if gout flares are infrequent (less than 2 per year) and no tophi are present, continuing current ULT is recommended over switching to Krystexxa.

VII. REFERENCES

1. Krystexxa [package insert]. Deerfield, IL: Horizon Therapeutics USA, Inc.; November 2022.
2. FitzGerald JD, Dalbeth N, Mikuls T, et al: 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken) 2020; 72(6):744-760.

KYMRIAH (tisagenlecleucel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)
      Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
   2. Adult Relapsed or Refractory (r/r) Diffuse Large B-cell Lymphoma
      Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
   3. Adult Relapsed or Refractory (r/r) Follicular Lymphoma (FL)
      Adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy.

      Limitation of Use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

B. Compendial Uses
   1. Pediatric B-cell ALL first relapse post hematopoietic stem cell transplant (HSCT)
   2. Histologic transformation of indolent lymphomas to DLBCL
   3. Human immunodeficiency virus (HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
   4. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
   5. Ph-negative or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy
   6. Ph-positive B-ALL with less than complete response or MRD+ at end of consolidation

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Previous treatment course with the requested medication or another CD19-directed chimeric antigen receptor (CAR) T-cell therapy
B. Inadequate and unstable kidney, liver, pulmonary and cardiac function
C. Active or latent hepatitis B, active hepatitis C or any active uncontrolled infection
D. Active graft versus host disease
E. Active inflammatory disorder

III. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For all indications: Chart notes, medical record documentation or claims history supporting previous lines of therapy

IV. CRITERIA FOR INITIAL APPROVAL

A. Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)
Authorization of 3 months may be granted for treatment of B-cell precursor ALL in members less than 26 years of age when the member meets any of the following:

1. Member has Philadelphia chromosome-negative disease that is refractory or has had 2 or more relapses
2. Member has Philadelphia chromosome-positive disease and meets any of the following:
    i. Member has refractory disease
    ii. Member had 2 or more relapses and has failed at least 2 tyrosine kinase inhibitors (TKIs) (e.g., bosutinib, dasatinib, imatinib, nilotinib, ponatinib).
    iii. Member has relapsed disease and is TKI intolerant
    iv. Member has experienced a relapse post-hematopoietic stem cell transplant (HSCT)
3. Ph-negative or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy
4. Ph-positive B-ALL with less than complete response or MRD+ at end of consolidation

B. Adult B-cell Lymphomas
Authorization of 3 months may be granted for treatment of B-cell lymphomas in members 18 years of age or older when all of the following criteria are met:

1. Member has any of the following B-cell lymphoma subtypes:
    i. Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma
    ii. Follicular lymphoma
    iii. Histologic transformation of indolent lymphomas to DLBCL
    iv. Diffuse large B-cell lymphoma (DLBCL)
    v. High-grade B-cell lymphomas (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
    vi. Human immunodeficiency virus (HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
    vii. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
2. The member has received prior treatment with two or more lines of systemic therapy
3. The member does not have primary central nervous system lymphoma.
4. Member has an ECOG performance status of 0 to 2 (member is ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Kymriah.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Acute lymphoblastic leukemia
4. NCCN Guideline: Pediatric acute lymphoblastic leukemia
5. NCCN Guideline: B-cell lymphomas
6. National Coverage Determination: Chimeric Antigen Receptor (CAR) T-cell Therapy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Kymriah are covered in addition to the following:

1. Pediatric B-cell ALL first relapse post hematopoietic stem cell transplant (HSCT)
2. Histologic transformation of indolent lymphomas to DLBCL

3. Human immunodeficiency virus (HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
4. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
5. Ph-negative or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy
6. Ph-positive B-ALL with less than complete response or MRD+ at end of consolidation

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Kymriah to treat compendial indications listed in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

All FDA-approved indications are covered according to the conditions outlined in National Coverage Determination Manual section 110.24 (Chimeric Antigen Receptor [CAR] T-cell Therapy).

VII. REFERENCES

1. Kymriah [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 17, 2023.
3. NCCN Clinical Practice Guidelines in Oncology® Acute Lymphoblastic Leukemia (Version 1.2022).© 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 17, 2023.
4. NCCN Clinical Practice Guidelines in Oncology® B-Cell Lymphomas (Version 2.2023).© 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 14, 2023.
5. National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24-Version 1). https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=374&ncdver=1&DocID=110.24&SearchType=Advanced&bc=EAAAAAIAAAAA&. Accessed April 17, 2023.
6. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-448.
7. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.

KYPROLIS (carfilzomib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Relapsed or Refractory Multiple Myeloma
1. Kyprolis is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with:
   i. Lenalidomide and dexamethasone; or
   ii. Dexamethasone; or
   iii. Daratumumab and dexamethasone; or
   iv. Daratumumab and hyaluronidase-fihj and dexamethasone; or
   v. Isatuximab and dexamethasone.
2. Kyprolis is indicated as a single agent for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

B. Compendial Uses
1. Multiple Myeloma
2. Waldenström macroglobulinemia/lymphoplasmacytic lymphoma
3. Systemic light chain amyloidosis

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Documentation of testing or laboratory results confirming presence of translocation t(11:14), where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Multiple Myeloma
Authorization of 12 months may be granted for treatment of multiple myeloma when the requested medication will used in any of the following regimens:
1. In combination with dexamethasone when the member has relapsed, refractory, or progressive disease
2. In combination with cyclophosphamide and dexamethasone
3. In combination with lenalidomide and dexamethasone
4. In combination with daratumumab, lenalidomide and dexamethasone
5. In combination with daratumumab and dexamethasone or daratumumab and hyaluronidase-fihj and dexamethasone when the member has relapsed, refractory, or progressive disease
6. In combination with pomalidomide and dexamethasone when the member has relapsed or progressive disease
7. In combination with cyclophosphamide, thalidomide, and dexamethasone when the member has relapsed or progressive disease
8. In combination with isatuximab-irfc and dexamethasone when the member has relapsed, refractory, or progressive disease
9. In combination with selinexor and dexamethasone when the member has relapsed or progressive disease
10. In combination with lenalidomide as maintenance therapy for symptomatic disease

11. In combination with bendamustine and dexamethasone when the member has received more than 3 prior therapies and has relapsed or refractory disease
12. In combination with venetoclax and dexamethasone when the member has relapsed or progressive disease has translocation t(11:14).
13. In combination with thalidomide and dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma
14. In combination with melphalan and prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma
15. As a single agent when the member has received one or more lines of therapy

B. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma
Authorization of 12 months may be granted for treatment of Waldenström macroglobulinemia/lymphoplasmacytic lymphoma.

C. Systemic Light Chain Amyloidosis
Authorization of 12 months may be granted for treatment of relapsed or refractory systemic light chain amyloidosis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen, and
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Kyprolis.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Waldenstrom macroglobulinemia/Lymphoplasmacytic lymphoma
4. NCCN Guideline: Systemic light chain amyloidosis
5. NCCN Guideline: Multiple myeloma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Kyprolis are covered in addition to the following:
    A. Waldenstrom macroglobulinemia/Lymphoplasmacytic lymphoma
    B. Systemic light chain amyloidosis

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Kyprolis to treat Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and

Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Kyprolis can be used as a component of CaRD (carfilzomib, rituximab, and dexamethasone) regimen as either primary therapy or for relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response.

Support for using Kyprolis to treat systemic light chain amyloidosis can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Kyprolis can be used as treatment for relapsed/refractory non-cardiac disease as either a single agent or in combination with dexamethasone.

Support for using Kyprolis to treat multiple myeloma in combination with agents not listed in the prescribing information can be found in the NCCN Drugs and Biologics Compendium and the Micromedex DrugDex database. Use of information in the NCCN Drugs and Biologics Compendium and the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Kyprolis [package insert]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc.; June 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 5, 2023.
3. DRUGDEX® System (electronic version). Micromedex Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com. Accessed October 5, 2023.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed October 5, 2023.

LAMZEDE (velmanase alfa-tycv)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Lamzede is indicated for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: alpha-mannosidase enzyme assay or genetic testing results supporting the diagnosis.
B. Continuation of therapy requests: documentation (e.g., chart notes, lab results) of a response to therapy (e.g., improvement in 3-minute stair climbing test [3MSCT] from baseline, improvement in 6-minute walking test [6MWT] from baseline, improvement in forced vital capacity [FVC, % predicted] from baseline, reduction in serum or urine oligosaccharide concentration from baseline).

III. CRITERIA FOR INITIAL APPROVAL

Alpha-mannosidosis
Authorization of 12 months may be granted for treatment of non-central nervous system manifestations of alpha-mannosidosis when the diagnosis is confirmed by either of the following:
A. A documented deficiency of alpha-mannosidase activity on enzyme assay, or
B. Genetic testing results documenting a mutation in the MAN2B1 gene.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., improvement in 3-minute stair climbing test [3MSCT] from baseline, improvement in 6-minute walking test [6MWT] from baseline, improvement in forced vital capacity [FVC, % predicted] from baseline, reduction in serum or urine oligosaccharide concentration from baseline).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lamzede.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. Presentation of a diagnostic algorithm from an international working group.
4. Alpha-Mannosidosis – Gene Reviews.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lamzede are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for use of genetic testing to confirm a diagnosis of alpha-mannosidosis can be found in a consensus statement from an international working group of experts. In Molecular Genetics and Metabolism, the diagnostic algorithm indicates that screening for alpha-mannosidosis is done by urine (less frequently serum) analysis of mannose-rich oligosaccharides and is often the first assay in the diagnostic path. Direct demonstration of low activity of acid alpha-mannosidase in blood leukocytes or cultured skin fibroblasts is considered to be the most reliable and diagnostic next step. Genetic analysis of MAN2B1 gene should be used to confirm the enzymatic diagnosis and may be used for prenatal diagnosis and genetic counselling of family members, but it should not replace biochemical testing.

VII. REFERENCES

1. Lamzede [package insert]. Cary, NC: Chiesi USA Inc.; February 2023.
2. Guffon, N, Tylki-Szymanska, A, Borgwardt, L, et al. Recognition of alpha-mannosidosis in paediatric and adult patients: Presentation of a diagnostic algorithm from an international working group. Mol Genet Metab. 2019; 126:470-474.
3. Malm D, Nilssen O. Alpha-Mannosidosis. In: GeneReviews. https://www.ncbi.nlm.nih.gov/books/NBK1396/ (Accessed on November 16, 2023).

SOMATULINE DEPOT (lanreotide acetate injection)
LANREOTIDE INJECTION (lanreotide acetate injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Somatuline Depot
      a. Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
      b. Treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
      c. Treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

   2. Lanreotide Injection
      a. Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
      b. Treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

B. Compendial Uses
   1. Neuroendocrine tumors (NETs):
      a. NETs of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors)
      b. NETs of the pancreas (islet cell tumors)
      c. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
   2. Pheochromocytoma/paraganglioma
   3. Hepatocellular carcinoma
   4. Thyroid carcinoma
   5. Thyroid stimulating hormone (TSH)-secreting pituitary adenoma
   6. Uterine leiomyoma
   7. Zollinger-Ellison syndrome

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions for acromegaly:

A. For initial approval: Laboratory report indicating high pretreatment insulin-like growth factor-1 (IGF-1) level and chart notes indicating an inadequate or partial response to surgery or radiotherapy or a clinical reason for not having surgery or radiotherapy.
B. For continuation: Laboratory report indicating normal current IGF-1 levels or chart notes indicating that the member's IGF-1 level has decreased or normalized since initiation of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Acromegaly
Authorization of 12 months may be granted for the treatment of acromegaly when all of the following criteria are met:
1. Member has a high pretreatment insulin-like growth factor-1 (IGF-1) level for age and/or gender based on the laboratory reference range.
2. Member had an inadequate or partial response to surgery or radiotherapy OR there is a clinical reason why the member has not had surgery or radiotherapy.

B. Carcinoid syndrome
Authorization of 12 months may be granted for treatment of carcinoid syndrome.

C. Neuroendocrine tumors (NETs)
1. Authorization of 12 months may be granted for treatment of NETs of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors).
2. Authorization of 12 months may be granted for treatment of NETs of the pancreas (islet cell tumors) including gastrinomas, glucagonomas, insulinomas, and VIPomas.
3. Authorization of 12 months may be granted for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

D. Pheochromocytoma and paraganglioma
Authorization of 12 months may be granted for treatment of pheochromocytoma/paraganglioma.

E. Hepatocellular carcinoma
Authorization of 12 months may be granted for treatment of hepatocellular carcinoma.

F. Thyroid carcinoma
Authorization of 12 months may be granted for treatment of thyroid carcinoma.

G. Thyroid stimulating hormone (TSH)-secreting pituitary adenoma
Authorization of 12 months may be granted for treatment of TSH-secreting pituitary adenoma.

H. Uterine leiomyoma
Authorization of 12 months may be granted for treatment of uterine leiomyoma.

I. Zollinger-Ellison syndrome
Authorization of 12 months may be granted for treatment of Zollinger-Ellison syndrome.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefits are defined as:
   1. Acromegaly: decreased or normalized IGF-1 level since initiation of therapy.
   2. All other indications: improvement or stabilization of clinical signs and symptoms since initiation of therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The package insert for Somatuline Depot.
2. The package insert for lanreotide injection.
3. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

4. The following professional guidelines:
   a. Medical guidelines for the clinical practice for the diagnosis and treatment of acromegaly from the American Association of Clinical Endocrinologists
   b. Acromegaly: an endocrine society clinical practice guideline from the Endocrine Society Clinical Guidelines Subcommittee
   c. NCCN Guideline: Neuroendocrine and adrenal tumors

After reviewing the information in the above resources, the FDA-approved indications listed in the package insert for Somatuline Depot (lanreotide) and the package insert for lanreotide injection are covered in addition to the following:

1. Neuroendocrine tumors (NETs)
   a. NETs of the gastrointestinal (GI) tract, lung and thymus
   b. NETs of the pancreas (islet cell tumors)
   c. gastroenteropancreatic neuroendocrine tumors (GEP-NETs).
2. Pheochromocytoma and paraganglioma
3. Hepatocellular carcinoma
4. Thyroid carcinoma
5. Thyroid stimulating hormone (TSH)-secreting pituitary adenoma
6. Uterine leiomyoma
7. Zollinger-Ellison syndrome

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Somatuline Depot and lanreotide to treat neuroendocrine tumors, pheochromocytoma, and paraganglioma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Somatuline Depot and lanreotide to treat hepatocellular carcinoma and thyroid carcinoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Somatuline Depot and lanreotide to treat thyroid stimulating hormone (TSH)-secreting pituitary adenomas can be found in a study by Gancel and colleagues (1994). In a small study (n=4), single injections of lanreotide 500 micrograms subcutaneously or 30 mg (slow-release formulation) intramuscularly resulted in significant decreases in plasma levels of thyroid-stimulating hormone (TSH) in patients with TSH-secreting pituitary adenomas and related hyperthyroidism. Plasma free thyroxine (fT4) and free triiodothyronine (fT3) were measured after slow-release lanreotide and also showed substantial reductions. Subsequent treatment with slow-release lanreotide 30 mg every 10 to 14 days in these patients was associated with progressive reductions in TSH, fT3, and fT4 for up to 6 months and a corresponding decrease in clinical symptoms. However, there was no change in pituitary adenoma volume during 3 to 6 months of therapy with these doses, which is in contrast to experience with octreotide (decrease in adenoma size in 30% of patients).

Support for using Somatuline Depot and lanreotide to reduce uterine and myoma volume can be found in a small study by DeLeo and colleagues (2001). Administration of lanreotide reduced uterine and myoma volume in 7 fertile women with uterine leiomyomata. Lanreotide 30 mg was administered as a depot formulation on the second day of the menstrual cycle and every 14 days for 3 months. After 3 months of therapy, mean basal uterine volume declined by 24% (p less than 0.05) while mean myoma volume declined by 42% (p less than 0.05) after therapy and 29% (p less than 0.5) 3 months after the end of treatment. During therapy, plasma

levels of estradiol and follicle-stimulating hormone did not change. However, mean growth hormone and insulin-like growth factor-I concentrations were significantly reduced (p less than 0.05).

Support for using Somatuline Depot and lanreotide to treat Zollinger-Ellison syndrome can be found in the National Comprehensive Cancer Network's guideline for neuroendocrine and adrenal tumors. The NCCN Guideline supports the use of lanreotide and octreotide long-acting release (LAR) for symptom and tumor control.

Support for utilizing a high pretreatment insulin-like growth factor-1 (IGF-1) as a diagnostic requirement and targeting IGF-1 in patients with acromegaly is supported by two professional guidelines.
According to Katznelson et al, the biochemical target goal is an age-normalized IGF-1. An age-normalized IGF-1 signifies control of acromegaly.
According to the Endocrine Society, IGF-1 should be measured and patients with elevated or equivocal serum IGF-1 levels should have the diagnosis confirmed by finding lack of suppression of growth hormone to less than 1 microgram/L following documented hyperglycemia during an oral glucose load. The Endocrine Society also supports the normalization of IGF-1 as the biochemical target goal of therapy with Somatuline Depot. Finally, the studies cited in the package insert for Somatuline Depot required patients to have an IGF-1 concentration 1.3 times or greater than the upper limit of the normal age-adjusted range.

VII. REFERENCES

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LEMTRADA (alemtuzumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Lemtrada is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

Limitations of Use
Lemtrada is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Multiple Sclerosis
Authorization of 30 days may be granted for treatment of relapsing forms of MS when the member had an inadequate response to two or more drugs for relapsing MS despite adequate duration of treatment or the member has a clinical reason to avoid such treatments.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 30 days may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Lemtrada.
B. Lemtrada is being used to treat an indication enumerated in Section II.
C. The member received the last dose of the previous course of treatment at least 12 months prior to the planned date of the next course of Lemtrada.
D. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lemtrada.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lemtrada are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCE

1. Lemtrada [package insert]. Cambridge, MA: Genzyme Corporation; January 2023.

LENMELDY (atidarsagene autotemcel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Lenmeldy is indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Chart notes, medical records, or lab results documenting all of the following:
A. PSLI, PSEJ, or ESEJ classification of MLD.
B. Variant(s) in the *ARSA* gene.
C. Deficiency of arylsulfatase A (ARSA) on biochemical testing.
D. Elevated sulfatide levels based on 24-hour urine collection, if applicable.

III. CRITERIA FOR INITIAL APPROVAL

Metachromatic Leukodystrophy (MLD)
Authorization of 3 months for a one-time administration may be granted for treatment of metachromatic leukodystrophy (MLD) when all of the following criteria are met:
A. Member must have one of the following types of MLD:
    1. Pre-symptomatic late infantile (PSLI).
    2. Pre-symptomatic early juvenile (PSEJ).
    3. Early symptomatic early juvenile (ESEJ).
B. The diagnosis was confirmed by all of the following:
    1. Biochemical testing documenting ARSA activity is below the normal range for the laboratory performing the test.
    2. The presence of two disease-causing ARSA alleles, either known or novel mutations, identified on genetic testing.
    3. If novel mutations are identified, a 24-hour urine collection showing elevated sulfatide levels.
C. Member has not received Lenmeldy or any other gene therapy previously.
D. Member does not have evidence of residual cells of donor origin if the member has received a prior allogeneic hematopoietic stem cell transplant (allo-HSCT).

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lenmeldy.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)

d. Lexi-Drugs
e. Clinical Pharmacology

3. Arylsulfatase A Deficiency - Gene Reviews.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lenmeldy are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Lenmeldy [package insert]. Boston, MA: Orchard Therapeutics North America.; March 2024.
2. Gomez-Ospina N. Arylsulfatase A Deficiency. 2006 May 30 [Updated 2024 Feb 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1130/. Accessed March 19, 2024.

LEQEMBI (lecanemab-irmb)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Leqembi is indicated for the treatment of Alzheimer's disease. Treatment with Leqembi should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Initial Requests:
   1. Medical records (e.g., chart notes) documenting the following:
      i. Diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.
   2. Presence of amyloid pathology documented by either of the following:
      i. Baseline positron emission tomography (PET) scan
      ii. Lumbar puncture results
   3. Clinician and member participation in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.
B. Continuation requests:
   1. Continued clinician and member participation in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a physician and/or clinical team who is participating in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

IV. CRITERIA FOR INITIAL APPROVAL

Alzheimer's Disease
Authorization of 6 months may be granted for treatment of Alzheimer's disease (AD) when all of the following criteria are met:

A. Member must have mild cognitive impairment due to AD or mild AD dementia.
B. Member must meet one of the following criteria:
   1. Have a positron emission tomography (PET) scan confirming the presence of amyloid pathology.
   2. Have results from a lumbar puncture confirming at least one of the following detected in cerebrospinal fluid (CSF) as determined by the lab assay:
      i. Presence of elevated phosphorylated tau (P-tau) protein and/or elevated total tau (T-tau) protein, and reduced beta-amyloid-42 (AB42)
      ii. Low AB42/AB40 ratio
      iii. Elevated P-Tau/AB42 ratio

iv. Elevated T-Tau/AB42 ratio

C. Member must currently be participating in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry with an appropriate clinical team and follow-up care via CMS-facilitated portal.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with Leqembi.
B. Leqembi is being used to treat an indication enumerated in Section IV.
C. The member continues to participate in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry with an appropriate clinical team and follow-up care via CMS-facilitated portal.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Leqembi.
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
3. National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leqembi are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Using Leqembi to treat mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease (AD) dementia is covered according to the conditions outlined in National Coverage Determination Manual section 200.3- Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Monoclonal antibodies directed against amyloid that are approved by the FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry. The information collected on the portal include the following:

- Individuals' clinical diagnosis (mild cognitive impairment or mild Alzheimer's disease dementia).
- Whether the individual is taking any anticoagulation or antiplatelet drugs.
- Results of the individual's amyloid positron emission tomography (PET) scan, cerebrospinal fluid (CSF) test, or other amyloid test.
- Specific anti-amyloid monoclonal antibody being administered.
- Whether there is evidence of adverse events such as brain swelling or hemorrhage referred to as ARIA-E or ARIAH-H.
- Results of tests of cognition and overall function that were used to diagnose and treat the individual with mild cognitive impairment or mild Alzheimer's disease dementia.

VIII. REFERENCES

1. Leqembi [package insert]. Nutley, NJ: Eisai Inc.; July 2023.

2. National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (200.3 – Version 1). https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1 Accessed July 8, 2023.
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LEQVIO (inclisiran)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Leqvio is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. LDL-C level must be dated within six months preceding the authorization request.
B. For members with clinical atherosclerotic cardiovascular disease (ASCVD), chart notes confirming clinical ASCVD (See Appendix A).
C. For members without clinical atherosclerotic cardiovascular disease (ASCVD), untreated (before any lipid lowering therapy) LDL-C level.
D. If member has contraindication or intolerance to statins, chart notes or medical documentation confirming the contraindication or intolerance (See Appendix B and C).

III. CRITERIA FOR INITIAL APPROVAL

Primary hyperlipidemia including heterozygous familial hypercholesterolemia (HeFH)
Authorization of 6 months may be granted for treatment of primary hyperlipidemia when one of the following criteria is met:
A. Member meets all of the following:
    1. Member has a history of clinical atherosclerotic cardiovascular disease (ASCVD) (See Appendix A).
    2. Member meets one of the following:
        i. Current LDL-C level ≥ 70 mg/dL after at least three months of treatment with a high-intensity statin. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used.
        ii. Current LDL-C level ≥ 70 mg/dL with a contraindication or intolerance to statins (See Appendix B and C).
    3. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (See Appendix B and C).
B. Member meets all of the following:
    1. Member had an untreated (before any lipid-lowering therapy) LDL-C level ≥ 190 mg/dL in the absence of a secondary cause.
    2. Member meets one of the following:
        i. Current LDL-C level ≥ 100 mg/dL after at least three months of treatment with a high-intensity statin. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used.
        ii. Current LDL-C level ≥ 100 mg/dL with a contraindication or intolerance to statins (See Appendix B and C).
    3. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (See Appendix B and C).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Leqvio.
B. Leqvio is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as achieved or maintained an LDL-C reduction (e.g., LDL-C is now at goal, robust lowering of LDL-C).
D. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (See Appendix B and C).

V. APPENDICES

APPENDIX A. Clinical ASCVD
- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization procedure (e.g., percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery)
- Stroke of presumed atherosclerotic origin
- Transient ischemic attack (TIA)
- Non-cardiac peripheral arterial disease (PAD) of presumed atherosclerotic origin (e.g., carotid artery stenosis, lower extremity PAD)
- Obstructive coronary artery disease (defined as fifty percent or greater stenosis on cardiac computed tomography angiogram or catheterization)
- Coronary Artery Calcium (CAC) Score ≥ 1000

APPENDIX B. Statin-associated muscle symptoms (SAMS) and statin re-challenge
- Score of 7 or higher on the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)
- Statin-associated elevation in creatine kinase (CK) level ≥ 10 times upper limit of normal (ULN)
  NOTE: Statin re-challenge is NOT required for members who have experienced an elevation of CK level ≥10 times ULN after receiving lipid-lowering therapy (LLT) with a statin.

APPENDIX C. Contraindications to statins
- Active liver disease, including unexplained persistent elevations in hepatic transaminase levels (e.g., alanine transaminase (ALT) level ≥ 3 times ULN)
- Pregnancy or planned pregnancy
- Breastfeeding

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Leqvio.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia from the American Heart Association
4. National Lipid Association recommendations for patient-centered management of dyslipidemia

5. 2018 AHA/ACC guideline on the management of blood cholesterol: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines
6. 2022 American College of Cardiology Expert Consensus Decision Pathway on the Role of Nonstatin therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leqvio and are included.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

In 3 large randomized studies, inclisiran significantly reduced LDL-C compared with placebo in patients who were on maximally tolerated statin doses but still required LDL-C lowering.

Support for using Leqvio in patients with heterozygous familial hypercholesterolemia is found in the package insert and the ORION-9 trial. The ORION-9 randomized trial (N=482) compared inclisiran with placebo in adults with heterozygous familial hypercholesterolemia and elevated LDL-C despite maximally tolerated doses of statin therapy with or without ezetimibe; patients receiving a PCSK9 monoclonal antibody were excluded. Patients were administered Leqvio as a subcutaneous injection on days 1, 90, 270 and 450. Patients had an LDL-C of at least 100 mg/dL (2.6 mmol/L). Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-39.7% vs +8.2%; difference, -47.9 percentage points; 95% CI, -53.5 to -42.3); mean absolute change in LDL-C levels was -59 versus +9.9 mg/dL (-1.5 vs +0.3 mmol/L). The time-averaged percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-38.1% vs +6.2%; difference, -44.3 percentage points; 95% CI, -48.5 to -40.1); mean absolute change was -56.9 vs +5.8 mg/dL (-1.5 vs +0.1 mmol/L). The percent change in PCSK9 level from baseline at day 510 was significantly greater with inclisiran versus placebo (-60.7% vs +17.7%); mean absolute change was -282.6 vs +54.5 mcg/L. Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-26.1% vs +6.8%), apolipoprotein B (-34% vs +2.9%), and non-HDL-C (-36.1% vs +7.5%). An LDL-C goal of less than 100 mg/dL was achieved by 65.3% versus 8.8% for inclisiran versus placebo and an LDL-C goal of less than 70 mg/dL was achieved by 40.8% with inclisiran versus 1.3% with placebo. Among 432 patients who had genetic testing, 80.8% had single LDLR variant, 5.3% had APOB variants, and 8.6% had a variant in LDLR and either APOB or PCSK9. Patients with LDLR variants had the highest mean baseline LDL-C level (160.8 mg/dL [4.2 mmol/L]). There were significant differences in mean percent change in LDL-C with inclisiran versus placebo from baseline at day 510 in patients with LDLR pathogenic variants (n=231; difference, -46 percentage points), LDLR probably pathogenic variants (n=17; difference, -48.3 percentage points), LDLR variants of uncertain significance (n=8; difference, -42.3 percentage points), APOB variants (n=23; difference, -52.1 percentage points), 2 variants (n=37; difference, -41.2 percentage points), no variants (n=115; difference, -59.2 percentage points), and no genetic testing (n=50; difference, -46.8 percentage points). There were no significant differences between inclisiran and placebo in the incidence of adverse events (76.8% vs 71.7%), but serious adverse events were significantly less frequent with inclisiran (7.5% vs 13.8%). Injection site reactions were more frequent with inclisiran (17% vs 1.7%) but were mostly mild.

The ORION-10 randomized trial (N=1561) compared inclisiran with placebo in adults with atherosclerotic cardiovascular disease (ASCVD) and elevated LDL-C despite maximally tolerated doses of statin therapy with or without additional lipid-lowering therapy; patients receiving a PCSK9 monoclonal antibody were excluded. Patients had an LDL-C of at least 70 mg/dL (1.8 mmol/L). Inclisiran 284 mg was administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450. Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-51.3% vs +1%; difference, -52.3 percentage points; 95% CI, -55.7 to -48.8); mean absolute change was -56.2 versus -2.1 mg/dL (-1.45 vs -0.05 mmol/L). The time-adjusted percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-51.3% vs +2.5%; difference, -53.8 percentage points; 95% CI, -56.2 to -51.3); mean absolute change was -53.7 vs -0.4 mg/dL (-1.39 vs -0.01 mmol/L). The percent change in PCSK9 levels from baseline at day 510 was significantly greater with inclisiran versus placebo (-69.8% vs +13.5%). Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-33.6% vs +0.4%), apolipoprotein B (-44.8% vs -1.7%), non-HDL-C (-47.4% vs -0.1%). LDL-C goals of less than 70 mg/dL and less than 100 mg/dL were achieved in 74.4% and 83.4% of inclisiran-treated patients compared with 15.3%

and 49.6% of placebo-treated patients. There were no significant differences between inclisiran and placebo in the incidence of adverse events (73.5% vs 74.8%) or serious adverse events (22.4% vs 26.3%). Injection site reactions were more frequent with inclisiran (2.6% vs 0.9%) but were mostly mild.

The ORION-11 randomized trial (N=1617) compared inclisiran with placebo in adults with ASCVD (approximately 87.5%) or an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or 10-year risk of cardiovascular event of at least 20% on Framingham Risk Score). Patients had elevated LDL-C despite maximally tolerated doses of statin therapy with or without additional lipid-lowering therapy, and patients receiving a PCSK9 monoclonal antibody were excluded. Patients with ASCVD had an LDL-C of at least 70 mg/dL (1.8 mmol/L), and patients with an ASCVD risk equivalent had an LDL-C of at least 100 mg/dL (2.6 mmol/L). Inclisiran 284 mg was administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450. Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-45.8% vs +4%; difference, -49.9 percentage points; 95% CI, -53.1 to -46.6); mean absolute change was -50.9 versus +1 mg/dL (-1.32 vs +0.03 mmol/L). The time-adjusted percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-45.8% vs +3.4%; difference, -49.2 percentage points; 95% CI, -51.6% to -46.8%); mean absolute change was -48.6 vs +0.3 mg/dL (-1.26 vs +0.01 mmol/L). The percent change in PCSK9 levels from baseline at day 510 was significantly greater with inclisiran versus placebo (-63.6% vs +15.6%). Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-28% vs +1.8%), apolipoprotein B (-38.2% vs +0.8%), and non-HDL-C (-41.2% vs +2.2%). LDL-C goals of less than 70 mg/dL and less than 100 mg/dL were achieved in 69.6% and 81.6% of inclisiran-treated patients compared with 12.9% and 52.7% of placebo-treated patients. There were no significant differences between inclisiran and placebo in the incidence of adverse events (82.7% vs 81.5%) or serious adverse events (22.3% vs 22.5%). Injection site reactions were more frequent with inclisiran (4.7% vs 0.5%) but were mostly mild.

VIII. REFERENCES

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LEUKINE (sargramostim)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Acute Myeloid Leukemia Following Induction Chemotherapy
   Leukine is indicated to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).
2. Autologous Peripheral Blood Progenitor Cell Mobilization and Collection
   Leukine is indicated in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.
3. Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation
   Leukine is indicated for acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).
4. Allogeneic Bone Marrow Transplantation (BMT)
   Leukine is indicated for the acceleration of myeloid reconstitution in adult and pediatric patients 2 years of age and older undergoing allogeneic BMT from human leukocyte antigens (HLA)-matched related donors.
5. Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure
   Leukine is indicated for the treatment of adult and pediatric patients 2 years and older who have undergone allogeneic or autologous BMT in whom neutrophil recovery is delayed or failed.
6. Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)
   Leukine is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

B. Compendial Uses
1. Prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies
2. Treatment of neutropenia and anemia in patients with myelodysplastic syndromes (MDS)
3. Acute myeloid leukemia
4. Agranulocytosis (non-chemotherapy drug induced)
5. Aplastic anemia
6. Neutropenia related to HIV/AIDS
7. Stem cell transplantation-related indications
8. Neuroblastoma
9. Severe chronic neutropenia (congenital, cyclic, or idiopathic)
10. Crohn’s disease
11. Malignant melanoma
12. Pulmonary alveolar proteinosis
13. Rhinocerebral mucormycosis
14. Hepatitis B vaccination, response enhancement
15. Metastatic renal cell carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Primary Prophylaxis of Febrile Neutropenia
Documentation of the member's diagnosis and chemotherapeutic regimen.

III. CRITERIA FOR INITIAL APPROVAL

A. Neutropenia in cancer patients receiving myelosuppressive chemotherapy
Authorization of 6 months may be granted for prevention or treatment of febrile neutropenia when both of the following criteria are met (1 and 2):
1. The member will not receive chemotherapy at the same time as they receive radiation therapy.
2. One of the following criteria is met (i or ii):
    i. The requested medication will be used for primary prophylaxis or secondary prophylaxis of febrile neutropenia in members with solid tumors or non-myeloid malignancies.
    ii. The requested medication will be used for treatment of high-risk febrile neutropenia (FN) in members who have any of the following prognostic factors that are predictive of clinical deterioration:
        a. Age greater than 65 years
        b. Being hospitalized at the time of the development of fever
        c. Sepsis syndrome
        d. Invasive fungal infection
        e. Pneumonia or other clinically documented infection
        f. Prolonged (neutropenia expected to last greater than 10 days) or profound (absolute neutrophil count less than 0.1×10^9/L) neutropenia
        g. Prior episodes of febrile neutropenia

B. Neuroblastoma
Authorization of 6 months may be granted for treatment of high-risk neuroblastoma when used with either of the following:
1. Dinutuximab (Unituxin), interleukin-2 (aldesleukin [Proleukin]), and isotretinoin (13-cis-retinoic acid [RA])
2. Naxitamab-gqgk (Danyelza)

C. Malignant melanoma
Authorization of 6 months may be granted for the treatment of malignant melanoma when used in either of the following settings:
1. For metastatic melanoma in combination with temozolomide, interferon-alfa 2b, and interleukin-2.
2. As adjuvant therapy in stage III or stage IV disease

D. Other indications
Authorization of 6 months may be granted for members with any of the following indications:
1. Myelodysplastic syndrome (anemia or neutropenia)
2. Acute myeloid leukemia
3. Agranulocytosis (non-chemotherapy drug induced)
4. Aplastic anemia
5. Neutropenia related to HIV/AIDS
6. Stem cell transplantation-related indications
7. Severe chronic neutropenia (congenital, cyclic, or idiopathic)
8. Hematopoietic Syndrome of Acute Radiation Syndrome:
   Treatment for radiation-induced myelosuppression following a radiological/nuclear incident
9. Moderately to severely active Crohn's disease
10. Pulmonary alveolar proteinosis
11. Rhinocerebral mucormycosis
12. Hepatitis B vaccination response enhancement
13. Renal cell carcinoma with pulmonary metastases when used with Interleukin-2 therapy

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization of 6 months may be granted for the treatment of renal cell carcinoma when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The member is receiving benefit from therapy. Benefit is defined as:
      i. No evidence of unacceptable toxicity while on current regimen
      ii. No evidence of disease progression while on the current regimen.

B. Authorization of 6 months may be granted for the treatment of pulmonary alveolar proteinosis when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The member is receiving benefit from therapy.

C. For all other diagnoses, all members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Leukine.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. The prescribing information for Unituxin and Danyelza.
4. NCCN Guideline: Hematopoietic growth factors
5. NCCN Guideline: Acute myeloid leukemia
6. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update.
7. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leukine are covered in addition to the following:
1. Prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies
2. Treatment of neutropenia and anemia in patients with myelodysplastic syndromes (MDS)
3. Acute myeloid leukemia
4. Agranulocytosis (non-chemotherapy drug induced)
5. Aplastic anemia
6. Neutropenia related to HIV/AIDS
7. Stem cell transplantation-related indications
8. Neuroblastoma
9. Severe chronic neutropenia (congenital, cyclic, or idiopathic)
10. Crohn’s disease
11. Malignant melanoma
12. Pulmonary alveolar proteinosis
13. Rhinocerebral mucormycosis
14. Hepatitis B vaccination, response enhancement
15. Metastatic renal cell carcinoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Leukine prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies can be found in the National Comprehensive Cancer Network's guideline for Hematopoietic Growth Factors. The NCCN Guideline for Hematopoietic Growth Factors supports the use of Leukine for treatment of chemotherapy-induced febrile neutropenia in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.

Support for using Leukine to treat neutropenia and anemia in patients with MDS can be found in several studies listed in the American Hospital Formulary System Drug Information reference. Leukine has been used in an effort to increase leukocyte counts in some adults with myelodysplastic syndrome (MDS) classified as refractory anemia (RA), refractory anemia with excess blasts (RAEB), or refractory anemia with excess blasts in transformation (RAEB-T). While the drug has shown some promise for this use, further study is needed to evaluate the benefits and risks of biosynthetic GM-CSF therapy in patients with MDS, pending accumulation of such data, this use generally should be limited to protocol conditions. MDS is a heterogeneous group of disorders and several factors (e.g., biologic characteristics of the leukemic clone, presence of an abnormal karyotype, or high initial leukemia burden) may result in considerable variation in response to sargramostim therapy. Use of sargramostim therapy in patients with MDS generally results in an increase in the absolute number of granulocytes and monocytes in most patients and an increase in the absolute number of eosinophils and lymphocytes in many patients. Although an increase in platelets and/or reticulocytes is evident in a few patients with MDS receiving sargramostim, platelet and reticulocyte counts are unaffected in most patients and the need for red blood cell transfusions generally is unchanged during therapy with the drug. Prolonged maintenance therapy with sargramostim appears necessary in patients with MDS since leukocyte counts return to pretreatment levels within 2–10 days after sargramostim is discontinued. Whether use of sargramostim in patients with MDS will alter (either increase or decrease) the rate of progression to AML or affect the usually fatal outcome of the disease is unclear and requires further study. The rate of progression to AML in untreated patients with MDS is approximately 10–20%, 40–50%, or 60–75% in those with RA, RAEB, or RAEB-T, respectively. There is concern, but no clear evidence indicated to date, that use of biosynthetic GM-CSFs may stimulate progression to AML in patients with MDS since in vitro evidence indicates that the drugs can stimulate the growth of myeloid leukemic blast cells and because an increase in the percentage of leukemic blasts in both bone marrow and peripheral blood has occurred in some patients with MDS receiving sargramostim. Although filgrastim (a biosynthetic G-CSF) also has been used in the treatment of MDS, the relative efficacy of these two hematologic growth factors has not been evaluated to date in controlled studies.

Support for using Leukine to treat acute myeloid leukemia can be found in the National Comprehensive Cancer Network's guideline for acute myeloid leukemia. The NCCN Guideline states there is no evidence for whether growth factors have a positive or negative impact on long-term outcome if used during consolidation. Growth factors may be considered as part of supportive care for postremission therapy. Growth factors are not routinely recommended in postremission therapy, except in life-threatening infections or when signs and symptoms of sepsis are present, and the leukemia is believed to be in remission.

Support for using Leukine to treat non-chemotherapy drug induced agranulocytosis can be found in a study by Rospond, Glowacki and Mailliard. Leukine has been used effectively in several patients to hasten recovery from sulfasalazine-associated agranulocytosis. A case report by Bjorkhom and colleagues found biosynthetic GM-CSFs can be used to treat methimazole-associated agranulocytosis in a patient with hyperthyroidism.

Support for using Leukine to treat aplastic anemia can be found several studies listed in the American Hospital Formulary Service Drug Information reference. Leukine has been used with some success in an effort to increase leukocyte counts in a limited number of adults and adolescents 15 years of age or older with moderate to severe aplastic anemia. Use of biosynthetic GM-CSFs such as Leukine in these patients resulted in an increase in ANCs that was sustained throughout the period of treatment and a transient increase in absolute eosinophil counts; most patients also had an increase in monocyte and lymphocyte counts. Erythrocyte and platelet counts and transfusion requirements generally were unaffected, although a few patients had increases in hemoglobin concentrations and/or platelet counts. Further study is needed to evaluate more fully use of sargramostim in aplastic anemia and to determine the optimum dosage and long-term safety and efficacy of the drug in these patients; pending accumulation of such data, this use generally should be limited to protocol conditions.

Support for using Leukine to treat neutropenia related to HIV/AIDS can be found several studies listed in the American Hospital Formulary Service Drug Information reference. Leukine has been used in patients with human immunodeficiency virus (HIV) infection in an effort to correct or minimize HIV-associated neutropenia and/or for the treatment of drug-induced neutropenia (e.g., neutropenia associated with use of zidovudine, interferon alfa, and/or cytotoxic chemotherapy) in HIV-infected patients. When used in patients with HIV infection, biosynthetic GM-CSFs effectively increase the number of neutrophils, monocytes, and eosinophils in most patients; however, the drugs appear to have no consistent effect on the absolute number of lymphocytes nor on the ratio of helper/inducer ($CD4^+$, $T4^+$) to suppressor/cytotoxic ($CD8^+$, $T8^+$) T cells.

Support for using Leukine for stem cell transplantation-related indications can be found in the American Society of Clinical Oncology clinical practice guideline. The ASCO guideline supports using Leukine for mobilization and after transplantation of autologous PBPC and after autologous or allogenic bone marrow transplant. Leukine should be started on the day of the bone marrow transplant and continue until the absolute neutrophil count is greater than 1.5x10(9)/L for three consecutive days. Leukine should be discontinued early or the dose of Leukine should be reduced by 50% if the absolute neutrophil count increases to greater than 20x10(9)/L.

Support for using Leukine to treat neuroblastoma can be found in the prescribing information for Unituxin and Danyelza. Unituxin is indicated, in combination with GM-CSF, interleukin-2, and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy. Danyelza is indicated, in combination with GM-CSF, for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

Support for using Leukine to treat severe chronic neutropenia (congenital, cyclic, or idiopathic) can be found in several studies listed in the American Hospital Formulary Service Drug Information reference. Sargramostim has been used with variable success in an effort to increase neutrophil counts in patients with various primary neutropenias, including congenital neutropenia, acquired idiopathic neutropenia, and glycogen storage disease type Ib. In addition, another biosynthetic GM-CSF, molgramostim, has been used with some success in patients with congenital neutropenia, cyclic neutropenia, acquired idiopathic neutropenia, or autoimmune neutropenia. While biosynthetic GM-CSFs may ameliorate the underlying neutropenia in certain patients with these conditions, this effect is unpredictable and not all patients with primary neutropenias respond to the drugs. Filgrastim (a biosynthetic G-CSF) has effectively increased neutrophil counts in some patients with severe congenital neutropenia, chronic idiopathic neutropenia, or cyclic neutropenia who did not respond to sargramostim therapy. In addition, it has been suggested that filgrastim may be more effective than sargramostim or other biosynthetic GM-CSFs in the treatment of primary neutropenia since filgrastim therapy results in more consistent increases in the neutrophil count and does not cause eosinophilia.
In a study in children 1–19 years of age with severe congenital neutropenia (Kostmann syndrome), sargramostim therapy resulted in an increase in the absolute granulocyte count in all patients. However, an increase in the ANC occurred in only one patient; in most patients, the increase in granulocytes during sargramostim therapy resulted from an increase in eosinophils or monocytes rather than neutrophils. When sargramostim was used in a few patients with glycogen storage disease type Ib, neutrophil counts increased during therapy with the drug and there was a decrease in inflammatory bowel symptoms. Use of sargramostim in a patient with idiopathic neutropenia also resulted in an increase in the neutrophil count.

Support for using Leukine to treat Crohn's disease can be found in a study by Korzenik and colleagues. Korzenik et al conducted a multicenter, randomized, placebo-controlled trial of 124 patients with Crohn's disease that concluded Leukine improved clinical response and remission when compared to placebo; however, the primary study endpoint was not met. Patients with moderate to severe active Crohn disease (defined as a score of 220 to 475 on the Crohn Disease Activity Index (CDAI)) and no prior history of sargramostim or filgrastim use were eligible for enrollment. Thirty-five percent of patients who were on stable doses of antibiotics and/or aminosalicylates for at least 4 weeks were included in the study; however, use of azathioprine, mercaptopurine, methotrexate, or oral or rectal glucocorticoids within 4 weeks or antitumor necrosis factor therapy within 12 weeks of study treatment was not permitted. Patients were randomized (2:1) to receive either sargramostim 6 micrograms/kilogram (mcg/kg) (n=81; median age, 36 years (yr); median CDAI score, 300) or placebo (n=43; median age, 41 yr; median CDAI score, 300) subcutaneously once daily for 56 days. Most patients in this study had previously received glucocorticoids (90%) and/or immunosuppressive medications (69%). At day 57, the primary endpoint of a clinical response defined as a

CDAI score decrease of at least 70 points from baseline was not significantly different between the 2 study arms (sargramostim arm, 54%; placebo arm, 44%; p=0.28). However, significantly more patients treated with sargramostim compared to placebo achieved the predefined secondary endpoints of clinical response defined as a CDAI score decrease of at least 100 points from baseline (48% versus (vs) 26%; p=0.01), remission at day 57 (defined as a CDAI score of 150 or less) (40% vs 19%; p=0.01), and improved quality of life (defined as an increase in the Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline) (28 vs 16 points; p=0.04) at day 57. Additionally, the median CDAI score was significantly lower at day 57 in the sargramostim-treated patients than in the placebo-treated patients (184 vs 240; p=0.02). At 30 days following treatment, evaluable patients who received sargramostim (n=53) had higher clinical response and remission rates compared to patients who received placebo (n=30) (CDAI score decrease of at least 70, 48% vs 28%; p=0.03; CDAI score decrease of at least 100, 42% vs 21%; p=0.02; remission, 33% vs 14%, p=0.02). Adverse events which occurred significantly (p less than 0.001) more often in the sargramostim arm compared to the placebo arm were injection-site reactions (90% vs 12%) and bone pain (37% vs 7%). Serious adverse events possibly related to sargramostim therapy occurred in 3 patients and included migraine; anorexia, weakness and lethargy; and right-sided weakness consistent with a demyelinating event.

Support for using Leukine to treat malignant melanoma can be found in a study by Spitler et al. In an open-label, multicenter, phase II trial, granulocyte-macrophage colony-stimulating factor (GM-CSF) may be a useful adjuvant therapy to prolong survival in patients with stage III or IV malignant melanoma. Patients who were clinically disease-free as a result of surgical resection of nodal or metastatic disease (n=48) were administered multiple 28-day cycles of subcutaneous GM-CSF 125 micrograms/square meter once daily for 14 days followed by 14 days of rest. Median treatment duration was 11.5 cycles (range 2 to 49). The response of these patients was compared to historical controls matched for age, sex, and the number of positive nodes in stage III patients, and the presence of visceral or nonvisceral metastases and site of metastasis in stage IV patients. Overall median survival was significantly longer in patients who received GM-CSF as compared to the historical controls (37.5 months and 12.2 months; p less than 0.001) with 1-year survival rates of 89% and 45% (p less than 0.001) and 2-year survival rates of 64% and 15% (p less than 0.001), respectively. These rates remained significant when patients were stratified according to stage III or IV disease. Overall disease-free survival was also significantly prolonged in the GM-CSF group (p=0.03), although there was no difference between groups when stratified by stage of disease. Adverse events included transient myalgias, weakness, mild fatigue, rash, and mild erythema at injection site

Support for using Leukine to treat pulmonary alveolar proteinosis can be found in a prospective, open-label study by Venkateshiah et al. Leukine therapy demonstrated good activity for the treatment of PAP. Patients (N=25; median age, 45 years; range, 21 to 57 years) with moderate disease were eligible for enrollment. Patients with a history of 2 or more lavages in the previous 4 months could also participate in the study at 3 months following their last whole-lung lavage (WLL) for a severe PAP exacerbation (n=21). Treatment consisted of Leukine 250 mcg/day subQ for the first month, 5 mcg/kg/day for the second month, and 9 mcg/kg/day for the third month. The Leukine dose could be increased to 12 mcg/kg/day at month 3, 15 mcg/kg/day at month 4, and 18 mcg/kg/day at month 5 if the patient was tolerating therapy but the response was suboptimal. When an adequate response was achieved, therapy could be continued for 3 to 12 months. At a mean follow-up of 39 +/- 17.3 months, 12 patients (48%) had an improvement in oxygenation with a 10 or greater mmHg decrease in the room air alveolar-arterial oxygen gradient (P(A-a)O2) (primary endpoint), with 8 patients not requiring WLL or home oxygen. Responders had significantly higher changes of PaO2, P(A-a)O2, diffusing capacity, total lung capacity, and 6-minute walk distance compared to patients who did not respond to Leukine therapy. At 6 months, the responders also had significantly improved quality of life scores (assessed by the Short Form-36 questionnaire) from baseline compared to non-responders for all measures except bodily pain. Common adverse effects with Leukine therapy included injection-site reactions (redness (n=18), itching (n=11), swelling (n=12)), shortness of breath (n=10), and fatigue (n=7).

Support for using Leukine to treat rhinocerebral mucormycosis in a case series by Garcia-Diaz, Palau and Pankey. Three patients with non-neutropenic rhinocerebral zygomycosis were successfully treated with the addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) to traditional surgical and medical treatment. A 51-year-old woman with diabetes and bronchial asthma requiring steroid therapy developed sinusitis with left- sided face pain, periorbital swelling, erythema, and blurred vision; her left pupil was dilated and unresponsive to light, and she had a black nasal discharge. She received amphotericin B and an intranasal ethmoidectomy and medial maxillectomy; cultures showed Rhizopus species. The disease worsened with extensive bony sequestrum of the left maxilla and palate which was treated surgically. GM-CSF was added (total 4500 mcg), and the patient recovered with no recurrence in 4 years of follow-up. A 65-year-old man with diabetes and asthmatic bronchitis requiring steroid therapy developed right-sided maxillary pain

and was found to have osteomyelitis. Histopathology of the maxillary bone was compatible with zygomycosis. He received amphotericin B but the disease progressed requiring debridement and right medial maxillectomy. His creatinine level increased; he received amphotericin B lipid complex (ABLC) and GM-CSF (425 mcg/day SC) and recovered with no recurrence with 3 years of follow-up. A 52-year-old woman with diabetes in ketoacidosis developed right eye pain and was found to have pansinusitis. She underwent right ethmoidectomy and removal of mucous membranes from right ethmoid and maxillary sinuses. Histology was consistent with zygomycosis. She received ABLC and GM-CSF 250 mcg/day SC but developed osteomyelitis of the right orbit requiring inferior orbitotomy. Histology was again consistent with zygomycosis. Treatment with ABLC and GM-CSF (total 45,000 micrograms) was discontinued approximately 5 months later as the patient was asymptomatic and biopsy showed no fungal elements; there was no recurrence in 2 years of follow-up.

Support for using Leukine for response enhancement following hepatitis B vaccination can be found in a study by Anandh, Bastani and Ballal. In chronic hemodialysis patients, granulocyte-macrophage colony-stimulating factor (GM-CSF) as adjuvant therapy resulted in enhanced seroconversion after hepatitis B vaccinations. In a randomized study (n=28), patients who received GM-CSF 4-5 micrograms per kilogram (mcg/kg) 24 hours before the first dose of their initial series of 3 hepatitis B vaccinations (40 mcg each) had significantly higher antibody titers, and the seroconversion rate (5 of 6 patients) was higher than those randomized to receive vaccine alone (2 of 6). Another group of patients who had failed to seroconvert after their primary series were randomized to receive or not receive GM-CSF 24 hours before a booster dose of 40 mcg of vaccine. Significantly (p less than 0.02) more patients seroconverted after receiving GM-CSF before their booster (7 of 8) than those receiving booster alone (2 of 8) and antibody titers were significantly higher (p less than 0.05) in those who received GM-CSF. Side effects were few and minor. The GM-CSF product used in this study was not mentioned.

Support for using Leukine to treat metastatic renal cell carcinoma can be found in a study by Hotton et al. Treatment with a combination of interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) did not produce total tumor burden shrinkage of 50% or greater, or pulmonary metastases reduction of 50% or greater, in any of the 14 evaluable patients with renal cell carcinoma and pulmonary metastases in a phase Ib/II trial. Median survival had not been reached at time of publication; 6 of 16 patients died during approximately 14 months of follow-up. Six patients with prior nephrectomy and 10 patients without prior nephrectomy were enrolled. The study was discontinued when a 60-year-old woman with a history of polycythemia vera developed a grade 4 thrombocytopenia and multiple cerebral hemorrhages and died. Postmortem examination revealed acute multifocal cerebral venous thrombosis, hemorrhagic venous infarcts, subdural and subarachnoid hemorrhage, and thrombosis of the superior vena cava and renal veins. Other toxicities included transient lymphopenia, eosinophilia, and elevated prothrombin times in 2 patients on warfarin therapy. Interleukin-2 was administered as a 96-hour continuous intravenous infusion on Days 1 through 4, days 8 through 11, and days 15 through 18 at a dose of 4.5 X 10(6) International Units/m(2) per day (27 of 31 total courses). GM-CSF was administered subcutaneously on days 8 through 19 at a dose of 1.25 mg/kg/day (12 of 31 courses) and 2.5 mg/kg/day (18 of 31 courses). There was a 14- to 19-day rest period between courses. The authors advise extreme caution with particular attention to early evidence of neurotoxicity in any further trials combining IL-2 and GM-CSF.

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LUPRON DEPOT 1-Month 7.5 mg
LUPRON DEPOT 3-Month 22.5 mg
LUPRON DEPOT 4-Month 30 mg
LUPRON DEPOT 6-Month 45 mg
(leuprolide acetate for depot suspension)

leuprolide acetate depot 3-month 22.5 mg

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Lupron Depot 1-Month 7.5 mg, Lupron Depot 3-Month 22.5 mg, leuprolide acetate depot 3-month 22.5 mg, Lupron Depot 4-Month 30 mg, and Lupron Depot 6-Month 45 mg are indicated in the treatment of advanced prostatic cancer.

B. Compendial Uses
1. Prostate cancer[3]
2. Ovarian Cancer - Malignant sex cord-stromal tumors
3. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
4. Induction of amenorrhea
5. Catamenial pneumothorax
6. Irritable bowel syndrome

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Prostate cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

B. Gender dysphoria
1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member has reached Tanner stage 2 of puberty or greater.
2. Authorization of 12 months may be granted for gender transition when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member will receive the requested medication concomitantly with gender-affirming hormones.

C. Ovarian cancer
Authorization of 12 months may be granted for treatment of malignant sex cord-stromal tumors.

D. Induction of amenorrhea
Authorization of 6 months may be granted for the induction of amenorrhea prior to undergoing bone marrow transplantation.

E. Catamenial pneumothorax
Authorization of 3 months may be granted for treatment of catamenial pneumothorax.

F. Irritable bowel syndrome
Authorization of 6 months may be granted for treatment of irritable bowel syndrome.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

A. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat ovarian cancer.
   3. The member is receiving benefit from therapy and has not experienced unacceptable toxicity.

B. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat prostate cancer.
   3. The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced unacceptable toxicity.

C. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat gender dysphoria
   3. The member is receiving benefit from therapy.

D. Authorization for 6 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to induce amenorrhea or to treat catamenial pneumothorax or irritable bowel syndrome.
   3. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg, and leuprolide acetate 22.5 mg.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Prostate cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg, and leuprolide acetate 22.5 mg are covered in addition to the following:
1. Prostate cancer
2. Ovarian Cancer - Malignant sex cord-stromal tumors
3. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
4. Induction of amenorrhea
5. Catamenial pneumothorax
6. Irritable bowel syndrome

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Lupron Depot to treat malignant sex cord-stromal tumors and prostate cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Lupron Depot for gender dysphoria can be found in the Endocrine Society Clinical Practice guideline for endocrine treatment of gender-dysphoric/gender-incongruent persons. The guidelines support GnRH agonist use in both transgender males and transgender females. Specific products are not listed; therefore, coverage is applied to the entire class of GnRH agonists.

Support for using Lupron Depot for gender dysphoria can also be found in the World Professional Association for Transgender Health (WPATH). According to the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, prescribing GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (defined as past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy. PATH also recommends beginning pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

WPATH recommends health care professionals prescribe progestins or a GnRH agonist for eligible transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.
WPATH also recommends health care professionals prescribe testosterone-lowering medications (including GnRH agonists) for eligible transgender and gender diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.
Support for using Lupron Depot to induce amenorrhea can be found in a study by Laufer and colleagues. Leuprolide was an effective way of inducing amenorrhea prior to women undergoing bone marrow transplantation. In 10 women, leuprolide 7.5 mg IM was given every 28 days before bone marrow transplantation and continued until the platelet count was greater than 50,000. Nine of the 10 women experienced amenorrhea. One woman with an "18-week" sized uterus containing a submucous myoma had continued spotting.

Support for using Lupron Depot to treat catamenial pneumothorax can be found in a case study published by Garris and Sokol. A 35-year-old nulligravida black female diagnosed with catamenial pneumothorax was successfully treated with depot leuprolide 7.5 mg monthly for 3 months followed by 3.75 mg monthly for 3 months. Prior to leuprolide treatment, the patient had undergone a right partial pleurectomy and partial right upper lobectomy without resolution of her catamenial respiratory symptoms. With leuprolide treatment, her symptoms resolved without recurrence in 2 years of followup. Because of severe vasomotor and emotional side effects which developed with leuprolide therapy, daily doses of continuous conjugated estrogens of 0.625 mg and medroxyprogesterone acetate 2.5 mg were instituted as a hormonal add-back regimen without apparent exacerbation of respiratory symptoms.

Support for using Lupron Depot to treat irritable bowel syndrome can be found in a study by Mathias et al. In a multicenter, double-blind study, women receiving leuprolide depot 7.5 mg monthly had improved abdominal pain and nausea as compared with placebo. Female patients with functional bowel disease were randomized to receive monthly intramuscular injections of either leuprolide 3.75 mg (n=32), leuprolide 7.5 mg (n=33), or placebo (n=35) for 16 weeks. Total symptom scores (pain, nausea, vomiting, bloating, anorexia, early satiety, altered bowel habits) were not statistically different for the leuprolide group compared with the placebo group. However, scores for pain and nausea for the leuprolide 7.5 mg group were significantly better than placebo at 16 weeks (p=0.044 and p less than 0.001, respectively). In both leuprolide groups, patient evaluations and physician global evaluations were statistically better (p less than 0.001).

VI. REFERENCES

1. Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45mg [package insert]. North Chicago, IL: AbbVie Inc.; April 2022.
2. Leuprolide acetate depot 22.5mg [package insert]. Warren, NJ: Cipla USA, Inc.; August 2018.
3. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed February 6, 2023.
4. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017:102(11):3869–3903.
5. Gender Identity Research and Education Society. Guidance for GPs and other clinicians on the treatment of gender variant people. UK Department of Health. Published March 10, 2008.
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7. DRUGDEX® System (electronic version). Truven Health Analytics, Ann Arbor, MI. Available at http://www.micromedexsolutions.com. Accessed February 7, 2023.
8. Laufer MR, Townsend NL, Parsons KE, et al: Inducing amenorrhea during bone marrow transplantation: a pilot study of leuprolide acetate. J Reprod Med 1997; 42(9):537-541.
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10. Mathias JR, Clench MH, Abell TL, et al: Effect of leuprolide acetate in treatment of abdominal pain and nausea in premenopausal women with functional bowel disease: a double-blind, placebo-controlled, randomized study. Dig Dis Sci 1998; 43(6):1347-1355.

FUSILEV (levoleucovorin) powder/solution
KHAPZORY (levoleucovorin) powder
levoleucovorin solution

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Levoleucovorin/Fusilev/Khapzory is indicated for rescue after high-dose methotrexate therapy in osteosarcoma.
   2. Levoleucovorin/Fusilev/Khapzory is indicated for diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination in adult and pediatric patients.
   3. Levoleucovorin/Fusilev/Khapzory is indicated for the treatment of adults with metastatic colorectal cancer in combination with fluorouracil.

B. Compendial Uses
   1. Rescue treatment after high-dose methotrexate therapy
   2. Combination with fluorouracil-based chemotherapy regimens

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted for any of the settings listed below when leucovorin is not an appropriate/available option at this time:
1. Rescue treatment after high-dose methotrexate therapy
2. Treatment of a folate antagonist overdose or impaired methotrexate elimination
3. Combination therapy with fluorouracil-based chemotherapy regimens

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. Leucovorin is not an appropriate/available option at this time.
D. The member is receiving benefit from therapy. Benefit is defined as:
   1. No evidence of unacceptable toxicity while on the current regimen and
   2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Fusilev, Khapzory, and levoleucovorin.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Fusilev, Khapzory, and levoleucovorin are covered in addition to the following:

1. Rescue treatment after high-dose methotrexate therapy
2. Combination with fluorouracil-based chemotherapy regimens

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Fusilev, Khapzory, and levoleucovorin when leucovorin is not available can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Fusilev [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; November 2020.
2. Levoleucovorin injection [package insert]. Princeton, NJ: Sandoz Inc.; December 2020.
3. Khapzory [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; March 2020.
4. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed July 7, 2023.

LIBTAYO (cemiplimab-rwlc)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Cutaneous Squamous Cell Carcinoma (CSCC)
      Libtayo is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.
   2. Basal Cell Carcinoma (BCC)
      a. Libtayo is indicated for the treatment of patients with locally advanced BCC previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
      b. Libtayo is indicated for the treatment of patients with metastatic BCC previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
   3. Non-Small Cell Lung Cancer (NSCLC)
      a. Libtayo, as a single agent, is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) $\geq$ 50%] as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations, and is:
         i. Locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
         ii. Metastatic
      b. Libtayo, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with NSCLC with no EGFR, ALK, or ROS1 aberrations and is:
         i. Locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
         ii. Metastatic

B. Compendial Uses
   1. Squamous cell skin cancer
   2. Basal cell skin cancer
   3. Non-small cell lung cancer
   4. Vulvar cancer
   5. Cervical cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.
B. Documentation of molecular testing for EGFR, KRAS, ALK, ROS1, BRAF, NTRK, MET, or RET genomic tumor aberrations, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous Squamous Cell Carcinoma (CSCC)
   1. Authorization of 12 months may be granted as single-agent neoadjuvant treatment of very high risk, locally advanced, unresectable, or regional cutaneous squamous cell carcinoma.

2. Authorization of 12 months may be granted for treatment of cutaneous squamous cell carcinoma when all of the following criteria are met:
    a. The disease is one of the following:
        1. Metastatic
        2. Locally advanced
        3. Recurrent
    b. The member is not a candidate for curative surgery or curative radiation
    c. The requested medication will be used as a single agent

B. Basal Cell Carcinoma (BCC)

Authorization of 12 months may be granted for single-agent treatment of basal cell carcinoma in members who have received a hedgehog pathway inhibitor (e.g., vismodegib [Erivedge], sonidegib [Odomzo]) or for whom a hedgehog pathway inhibitor is not appropriate and when any of the following criteria are met:

1. Member has locally advanced disease
2. Member has nodal disease and surgery is not feasible
3. Member has metastatic disease

C. Non-Small Cell Lung Cancer (NSCLC)

Authorization of 12 months may be granted for treatment of recurrent, advanced, or metastatic non-small cell lung cancer (NSCLC) when any of the following criteria are met:

1. The requested medication will be used as first-line therapy and the tumor does not have EGFR exon 19 deletions or L858R mutations, ALK rearrangements, or ROS1 aberrations (unless testing is not feasible due to insufficient tissue) as either:
    a. A single agent for tumors with a high PD-L1 expression [Tumor Proportion Score (TPS) $\geq$ 50%], or
    b. In combination with platinum-based chemotherapy
2. The requested medication will be used as maintenance therapy following first-line cemiplimab-rwlc therapy and the tumor does not have EGFR exon 19 deletions or L858R mutations, ALK rearrangements, or ROS1 aberrations (unless testing is not feasible due to insufficient tissue) as either:
    a. A single agent, or
    b. In combination with pemetrexed
3. The requested medication will be used as subsequent therapy in combination with platinum-based chemotherapy.

D. Vulvar Cancer

Authorization of 12 months may be granted as subsequent therapy for advanced or recurrent/metastatic vulvar cancer when the requested medication will be used as a single agent.

E. Cervical Cancer

Authorization of 12 months may be granted as subsequent therapy for recurrent or metastatic cervical cancer when the requested medication will be used as a single agent.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Basal Cell Carcinoma or Cutaneous Squamous Cell Carcinoma

Authorization for 12 months (up to 24 months total) may be granted for all members (including new members) who are continuing with the requested medication when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat basal cell carcinoma or cutaneous squamous cell carcinoma
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen and
    b. No evidence of disease progression while on the current regimen

B. All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section III
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen and
    b. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Libtayo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Squamous cell skin cancer
4. NCCN Guideline: Basal cell skin cancer
5. NCCN Guideline: Non-small cell lung cancer
6. NCCN Guideline: Vulvar cancer
7. NCCN Guideline: Cervical cancer

A. After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Libtayo are covered in addition to the following: Recurrent or regional cutaneous squamous cell carcinoma
B. Recurrent basal cell carcinoma
C. Additional non-small cell lung cancer scenarios that are not covered in the package insert
D. Vulvar cancer
E. Cervical cancer

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for recurrent or regional cutaneous squamous cell carcinoma, recurrent basal cell carcinoma, non-small cell lung cancer, vulvar cancer, and cervical cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Libtayo [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; April 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed December 13, 2023.

LOQTORZI (toripalimab-tpzi)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. Loqtorzi is indicated, in combination with cisplatin and gemcitabine, for first-line treatment of adults with metastatic or with recurrent locally advanced nasopharyngeal carcinoma (NPC).
B. Loqtorzi is indicated, as a single agent, for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Nasopharyngeal carcinoma (NPC)
Authorization of 12 months may be granted when either of the following criteria are met:

A. The requested medication will be used in combination with cisplatin and gemcitabine for the first-line treatment of metastatic or recurrent locally advanced NPC.
B. The requested medication will be used as a single agent for treatment of recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months (for up to 24 months total when being used as first line therapy) may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen, and
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Loqtorzi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Head and neck cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Loqtorzi are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Loqtorzi [package insert]. Redwood City, CA: Coherus BioSciences, Inc; October 2023.

LUCENTIS (ranibizumab)
BYOOVIZ (ranibizumab-nuna)
CIMERLI (ranibizumab-eqrn)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Lucentis, Byooviz and Cimerli are indicated for:
1. Neovascular (wet) age-related macular degeneration
2. Macular edema following retinal vein occlusion
3. Myopic choroidal neovascularization

Lucentis and Cimerli are also indicated for:
1. Diabetic macular edema
2. Diabetic retinopathy

B. Compendial Uses
Retinopathy of prematurity

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Neovascular (wet) age-related macular degeneration
Authorization of 12 months may be granted for treatment of neovascular age-related macular degeneration.

B. Macular edema following retinal vein occlusion
Authorization of 12 months may be granted for treatment of macular edema following retinal vein occlusion.

C. Diabetic macular edema
Authorization of 12 months may be granted for the treatment of diabetic macular edema.

D. Diabetic retinopathy
Authorization of 12 months may be granted for the treatment of diabetic retinopathy.

E. Myopic choroidal neovascularization
Authorization of 12 months may be granted for the treatment of myopic choroidal neovascularization.

F. Retinopathy of prematurity
Authorization of 12 months may be granted for the treatment of retinopathy of prematurity.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when ALL of the following criteria are met:
A. The member is currently receiving therapy with the requested product.
B. The requested product is being used to treat an indication enumerated in Section II.
C. The medication has been effective for treating the diagnosis or condition.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lucentis, Byooviz, and Cimerli
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lucentis, Byooviz and Cimerli are covered in addition to retinopathy of prematurity.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for retinopathy of prematurity can be found in a retrospective single center study of 128 infants with Type 1 ROP and 18-month follow-up examinations found recurrence rates of 16.7% (1 of 6 patients) with intravitreal ranibizumab 0.25 mg and 8.3% (1 of 12 patients) with intravitreal bevacizumab 0.625 mg following initial regression within 48 hours in all patients who received either ranibizumab or bevacizumab. Recurrence was defined as recurrent plus or preplus disease or neovascularization, or progression of traction. In a third group of 36 patients who received LPC therapy, initial regression occurred in 1 to 2 weeks except in 5 patients who required retreatment with LPC at 10 days. Differences in the ranibizumab, bevacizumab, and LPC groups at baseline were found in birth weight (840, 841, and 1112 grams, respectively), number of patients with Stage 3 disease (16.7%, 16.7%, and 61.1%, respectively), APROP (83.3%, 83.3%, and 19.4%, respectively), and Zone II disease (66.7%, 83.3%, and 88.9%, respectively). A fourth group of 74 patients with spontaneously regressed ROP was included. The two patients who recurred after ranibizumab or bevacizumab therapy achieved successful regression following subsequent LPC therapy. Mean total vascularization time was significantly shorter with ranibizumab (61.8 weeks of PMA) compared with bevacizumab (73 weeks of PMA). Following LPC, one patient experienced exudative retinal detachment and nystagmus in both eyes and one patient had macular ectopia and nystagmus; no ocular complications were noted in other groups other than transient preretinal hemorrhages.

Ranibizumab compared with laser photocoagulation (LPC), did not demonstrate a significant difference for the primary outcome (composite of survival with no active retinopathy, no unfavorable structural outcomes, or need for a different treatment modality at 24 weeks; 80% vs 66%; OR, 2.19; 95% CI, 0.99 to 4.82) in the randomized RAINBOW trial in infants with retinopathy of prematurity (ROP; N=214). Included infants (median gestational age 26 weeks) had bilateral ROP zone I stage 1+, 2+, 3, or 3+, zone II stage 3+, or aggressive posterior ROP (AP-ROP). Infants with zone II stage 2+ were excluded. Treatment success (alive and without treatment switch and unfavorable structural outcome or active ROP at day 169) was not significantly different between groups; achieved in 80% with ranibizumab 0.2 mg, 75% with ranibizumab 0.1 mg, and 66% with laser therapy. In a post-hoc analysis accounting for potential confounders (gestational age, geographical region, and gender) the primary outcome was significant for ranibizumab 0.2 mg compared with laser (OR 2.32; 95% CI, 1.04 to 5.16). There was no significant between-group difference in the plasma vascular endothelial growth factor (VEGF) levels. There was 1 death associated with ranibizumab 0.1 mg or the procedure due to respiratory failure. Interventions included a single bilateral intravitreal dose of ranibizumab 0·2 mg, 0·1 mg, or laser therapy. The ranibizumab groups were permitted up to 2 additional treatments in each eye at a minimum

of 28-day intervals and in the laser group supplementary treatment to skip lesions was allowed up to day 11. Additional treatments were needed in 31% with ranibizumab 0.2 mg , 31% with ranibizumab 0.1 mg, and 19% with laser therapy.

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LUMIZYME (alglucosidase alfa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Lumizyme is indicated for patients with Pompe disease (acid alpha-glucosidase [GAA] deficiency).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: acid alpha-glucosidase enzyme assay or genetic testing results supporting diagnosis.
B. Continuation or therapy: chart notes documenting a positive response to therapy.

III. CRITERIA FOR INITIAL APPROVAL

Pompe disease
Authorization of 12 months may be granted for treatment of Pompe disease when the diagnosis of Pompe disease was confirmed by enzyme assay demonstrating a deficiency of acid alpha-glucosidase enzyme activity or by genetic testing.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, walking capacity, cardiorespiratory function, decrease in left ventricular mass index (LVMI), delay in death).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lumizyme.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Glycogen Storage Disease Type II (Pompe Disease), Gene Reviews article

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lumizyme are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assays and genetic testing to diagnose Pompe disease can be found in a Gene Reviews article. The diagnosis of Pompe disease is established in a patient with either deficiency of acid alpha-glucosidase enzyme activity or biallelic pathogenic variants in GAA on molecular genetic testing.

VII. REFERENCES

1. Lumizyme [package insert]. Cambridge, MA: Genzyme Corporation; May 2022.
2. Leslie N, Tinkle BT. Glycogen Storage Disease Type II (Pompe Disease). GeneReviews 2013 May 9.

LUNSUMIO (mosunetuzumab-axgb)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Lunsumio is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

B. Compendial Use
Follicular lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Follicular Lymphoma
Authorization of 12 months may be granted for treatment of follicular lymphoma when both of the following criteria are met:
1. The disease had a partial or no response to treatment or the disease is relapsed or progressive
2. The member has tried at least 2 prior lines of systemic therapy

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lunsumio.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lunsumio are covered in addition to follicular lymphoma that did not respond to prior therapy, or partially responded to prior therapy.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Lunsumio to treat follicular lymphoma that did not respond to prior therapy or partially responded to prior therapy can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Lunsumio [package insert]. South San Francisco, CA: Genentech, Inc.; December 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 2, 2023.

LUPRON DEPOT 3.75 mg
LUPRON DEPOT-3 Month 11.25 mg
(leuprolide acetate for depot suspension)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Endometriosis
   Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot 3.75 mg monthly and Lupron Depot-3 Month 11.25 mg with norethindrone acetate 5 mg daily are also indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

   Use of norethindrone acetate in combination with Lupron Depot 3.75 mg and Lupron Depot 11.25 mg is referred to as add-back therapy, and is intended to reduce the loss of bone mineral density (BMD) and reduce vasomotor symptoms associated with use of Lupron Depot 3.75 mg and Lupron Depot 11.25 mg.

2. Uterine Leiomyomata (Fibroids)
   When used concomitantly with iron therapy, Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary. The clinician may wish to consider a one-month trial period on iron alone, as some women will respond to iron alone. Lupron Depot may be added if the response to iron alone is considered inadequate.

   Limitations of Use:
   For endometriosis: The total duration of therapy with Lupron Depot 3.75 mg and 11.25 mg plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density.

   For uterine leiomyomata: Lupron Depot 3.75 mg and 11.25 mg is not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids.

B. Compendial Uses

1. Breast cancer
2. Ovarian Cancer
   i. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
   ii. Carcinosarcoma (Malignant mixed Müllerian tumors)
   iii. Grade 1 endometrioid carcinoma
   iv. Low-grade serous carcinoma
   v. Mucinous carcinoma of the ovary
   vi. Clear cell carcinoma of the ovary
3. Salivary gland tumors
4. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
5. Preservation of ovarian function
6. Prevention of recurrent menstrual related attacks in acute porphyria
7. Adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome
8. Catamenial pneumothorax

9. Irritable bowel syndrome
10. Premenstrual syndrome
11. Use in combination with growth hormone for children with growth failure and advancing puberty
12. Induction of amenorrhea

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Endometriosis

Authorization of up to 6 months (one treatment course) may be granted to members for initial treatment of endometriosis.

B. Uterine leiomyomata (fibroids)

Authorization of up to 3 months may be granted for initial treatment of uterine leiomyomata (fibroids) when either of the following criteria is met:

1. Member has anemia due to uterine leiomyomata, or
2. Lupron Depot will be used prior to surgery for uterine leiomyomata.

C. Breast cancer

Authorization of 12 months may be granted for treatment of hormone receptor-positive breast cancer.

D. Ovarian cancer

Authorization of 12 months may be granted for treatment of the following types of ovarian cancer:

1. Epithelial ovarian cancer
2. Fallopian tube cancer
3. Primary peritoneal cancer
4. Grade 1 endometrioid carcinoma
5. Low-grade serous carcinoma
6. Carcinosarcoma (malignant mixed Müllerian tumors)
7. Mucinous carcinoma of the ovary
8. Clear cell carcinoma of the ovary

E. Salivary gland tumors

Authorization of 12 months may be granted for treatment of recurrent salivary gland tumors when the tumor is androgen receptor positive.

F. Gender dysphoria

1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when both of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member has reached Tanner stage 2 of puberty or greater.
2. Authorization of 12 months may be granted for gender transition when both of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member will receive the requested medication concomitantly with gender-affirming hormones.

G. Preservation of ovarian function

Authorization of 3 months may be granted for preservation of ovarian function when the member is premenopausal and undergoing chemotherapy.

H. Prevention of recurrent menstrual related attacks in acute porphyria

Authorization of 12 months may be granted for prevention of recurrent menstrual related attacks in members with acute porphyria when the requested medication is prescribed by or in consultation with a physician experienced in the management of porphyrias.

I. Adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome
Authorization of 12 months may be granted for treatment of ACTH-dependent Cushing's syndrome.

J. Catamenial pneumothorax
Authorization of 3 months may be granted for treatment of catamenial pneumothorax.

K. Irritable bowel syndrome
Authorization of 6 months may be granted for treatment of irritable bowel syndrome.

L. Premenstrual syndrome
Authorization of 3 months may be granted for treatment of premenstrual syndrome.

M. Advancing puberty and growth failure
Authorization of 12 months may be granted for treatment of advancing puberty and growth failure in a pediatric member when used in combination with growth hormone.

N. Induction of amenorrhea
Authorization of 6 months may be granted for the induction of amenorrhea prior to undergoing bone marrow transplantation.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

A. Authorization for 6 months (for a lifetime maximum of 12 months total) may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat endometriosis.
   3. The member is receiving benefit from therapy.
   4. The member has had a recurrence of symptoms.
   5. The member has a bone mineral density within normal limits.

B. Authorization for 3 months (for a lifetime maximum of 6 months total) may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. Lupron Depot is being used to treat uterine leiomyomata (fibroids).
   3. The member is receiving benefit from therapy.
   4. The member meets one of the following:
      i. The member has anemia due to uterine leiomyomata.
      ii. The requested medication will be used prior to surgery for uterine leiomyomata.

C. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat breast cancer, ovarian cancer, or salivary gland tumors.
   3. The member is receiving benefit from therapy and has not experienced unacceptable toxicity.

D. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat one of the following indications enumerated in Section II:
      i. Gender dysphoria
      ii. Prevention of recurrent menstrual related attacks in acute porphyria
      iii. ACTH-dependent Cushing's syndrome
      iv. Advancing puberty and growth failure in combination with growth hormone

3. The member is receiving benefit from therapy.

E. Authorization for 6 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat one of the following indications enumerated in Section II:
      i. Irritable bowel syndrome
      ii. Induction of amenorrhea
   3. The member is receiving benefit from therapy.

F. Authorization for 3 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat one of the following indications enumerated in Section II:
      i. Preservation of ovarian function
      ii. Catamenial pneumothorax
      iii. Premenstrual syndrome
   3. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Lupron Depot 3.75 mg and 11.25 mg.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Head and neck cancers
4. NCCN Guideline: Breast cancer
5. NCCN Guideline: Ovarian cancer/fallopian tube cancer/primary peritoneal cancer
6. Management of symptomatic uterine leiomyomas: ACOG Practice Bulletin No. 228. American College of Obstetricians and Gynecologists
7. Therapeutic management of uterine fibroid tumors: updated French guidelines
8. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline
9. Guidance for GPs and other clinicians on the treatment of gender variant people
10. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, 8th version
11. British and Irish Porphyria Network. Best practice guidelines on clinical management of acute attacks of porphyria and their complications.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lupron Depot 3.75 mg and 11.25 mg are covered in addition to the following:
1. Breast cancer
2. Ovarian Cancer
   i. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
   ii. Carcinosarcoma (Malignant mixed Müllerian tumors)
   iii. Grade 1 endometrioid carcinoma
   iv. Low-grade serous carcinoma
   v. Mucinous carcinoma of the ovary
   vi. Clear cell carcinoma of the ovary
3. Salivary gland tumors
4. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
5. Preservation of ovarian function
6. Prevention of recurrent menstrual related attacks in acute porphyria

7. Adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome
8. Catamenial pneumothorax
9. Irritable bowel syndrome
10. Premenstrual syndrome
11. Use in combination with growth hormone for children with growth failure and advancing puberty
12. Induction of amenorrhea

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Lupron Depot to treat breast cancer, ovarian cancer, and salivary gland tumors can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Lupron Depot for gender dysphoria can be found in the Endocrine Society Clinical Practice guideline for endocrine treatment of gender-dysphoric/gender-incongruent persons. The guidelines support GnRH agonist use in both transgender males and transgender females. Specific products are not listed; therefore, coverage is applied to the entire class of GnRH agonists.

Support for using Lupron Depot for gender dysphoria can also be found in the World Professional Association for Transgender Health (WPATH). According to the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, prescribing GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (defined as past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy. PATH also recommends beginning pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

WPATH recommends health care professionals prescribe progestins or a GnRH agonist for eligible transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.
WPATH also recommends health care professionals prescribe testosterone-lowering medications (including GnRH agonists) for eligible transgender and gender diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.

Support for using Lupron Depot for preservation of ovarian function can be found in the ASCO Clinical Practice Guidelines for fertility preservation in patients with cancer. The guideline indicates gonadotropin-releasing hormone receptor agonist therapy may be offered to young women, especially those with breast cancer, in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency when proven fertility preservation methods (i.e., oocyte, embryo, or ovarian tissue cryopreservation) are not feasible. Gonadotropin-releasing hormone receptor agonists should not be used in place of proven fertility preservation methods.

Support for using Lupron Depot to prevent recurrent menstrual-related attacks in acute porphyria can be found in the British and Irish Porphyria Network on clinical management of acute attacks of porphyria and their complications (Stein et al., 2012). In women with recurrent premenstrual attacks of porphyria, GnRH analogues can be administered to prevent ovulation. A number of preparations are available (busrelin, goserelin, histrelin, leuprorelin or triptorelin) and published studies have reported use of differing regimens, sometimes in extremely low doses. As an example, Zoladex 3.6 (containing goserelin acetate 3.6 mg) a long acting analogue of GnRH, can be given as an implant by subcutaneous injection into the anterior abdominal wall every 28 days, with the first injection being given during the first few days of the menstrual cycle. Administration of GnRH analogues may induce a hormone surge that can trigger an acute attack. Side-effects include depression, hot flushes, reduced libido, osteoporosis, and other menopausal symptoms. These can be reduced by use of a low dose estrogen patch. Pretreatment assessment of skeletal health (including bone

mineral density [BMD] determination) should be arranged with regular gynecology review and annual BMD while treatment continues. Treatment with GnRH analogues should be reviewed after one year.

Support for using Lupron Depot to treat adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome can be found in a case report by Lacroix, Hamet and Boutin (1999). A 63-year-old woman with bilateral adrenal hyperplasia and corticotropin-independent Cushing syndrome had her symptoms reversed with leuprolide therapy. The woman presented with hypertension, numbness, proximal muscle weakness of the lower extremities, hot flashes, weight gain, and a decrease in concentration and memory. Her Cushing syndrome had been manifested transiently during her pregnancies and became constant after menopause. It was determined that her Cushing syndrome resulted from corticotropin-independent bilateral macronodular hyperplasia. Her cortisol production was stimulated by gonadotropin-releasing hormone, and luteinizing hormone, and by drugs that activate serotonin 5-hydroxy-tryptamine receptors. With long-term leuprolide therapy (3.75 mg IM every 4 weeks), her urinary cortisol dropped into the normal range and her morning and evening plasma cortisol concentrations normalized. Her weight decreased and her blood pressure became normal.

Support for using Lupron Depot to treat catamenial pneumothorax can be found in a case study published by Garris and Sokol (1994). A 35-year-old nulligravida black female diagnosed with catamenial pneumothorax was successfully treated with depot leuprolide 7.5 mg monthly for 3 months followed by 3.75 mg monthly for 3 months. Prior to leuprolide treatment, the patient had undergone a right partial pleurectomy and partial right upper lobectomy without resolution of her catamenial respiratory symptoms. With leuprolide treatment, her symptoms resolved without recurrence in 2 years of follow-up. Because of severe vasomotor and emotional side effects which developed with leuprolide therapy, daily doses of continuous conjugated estrogens of 0.625 mg and medroxyprogesterone acetate 2.5 mg were instituted as a hormonal add-back regimen without apparent exacerbation of respiratory symptoms.

Support for using Lupron Depot to treat irritable bowel syndrome can be found in a study by Mathias et al. (1998). In a multicenter, double-blind study, women receiving leuprolide depot 7.5 mg monthly had improved abdominal pain and nausea as compared with placebo. Female patients with functional bowel disease were randomized to receive monthly intramuscular injections of either leuprolide 3.75 mg (n=32), leuprolide 7.5 mg (n=33), or placebo (n=35) for 16 weeks. Total symptom scores (pain, nausea, vomiting, bloating, anorexia, early satiety, altered bowel habits) were not statistically different for the leuprolide group compared with the placebo group. However, scores for pain and nausea for the leuprolide 7.5 mg group were significantly better than placebo at 16 weeks (p=0.044 and p less than 0.001, respectively). In both leuprolide groups, patient evaluations and physician global evaluations were statistically better (p less than 0.001).

Support for using Lupron Depot to treat premenstrual syndrome can be found in a study by Schmidt and colleagues (1998). Ovarian suppression with leuprolide treatment can reduce the symptoms of premenstrual syndrome (PMS) in some women. Twenty women with PMS, substantiated by symptom diaries for 3 menstrual cycles, were randomized to receive 3 monthly IM injections of either leuprolide depot 3.75 mg or an equal amount of saline (placebo) in a double-blind manner. Women having 2 normal menstrual periods and no hot flashes were presumed to be taking placebo. Their codes were broken, and they were then offered the opportunity to take leuprolide in an open-label manner. For the leuprolide group, average PMS symptom scores at week 4 of treatment were significantly lower than at week 4 of baseline and lower than those in the group receiving placebo (p values all less than 0.05). No woman responded to placebo with a lessening of symptoms. Ten of 18 women who received leuprolide under either double-blind or open-label conditions responded.

Support for using Lupron Depot in combination with growth hormone for children with growth failure and advancing puberty can be found in a study by Mericq et al. (2000). Combination treatment with growth hormone (GH) and luteinizing hormone-releasing hormone analog (LHRH-A) in pubertal growth hormone-deficient patients resulted in a significant decrease in the rate of bone maturation and an increase in final height. The prospective trial randomized 21 growth hormone-deficient pediatric patients to GH plus LHRH-A or GH alone for 3 years. A significant decrease in bone age maturation was observed for the combination treatment group (1.5 years) compared with the GH only group (4.2 years; p less than 0.05). The delay in bone age maturation produced a significant increase in final height in the combination group (p less than 0.05).

Support for using Lupron Depot to induce amenorrhea prior to undergoing bone marrow transplantation can be found in a study by Laufer and colleagues (1997). Leuprolide was an effective way of inducing amenorrhea prior to women undergoing bone marrow transplantation. In 10 women, leuprolide 7.5 mg IM was given every 28 days before bone marrow transplantation and continued until the platelet count was greater than 50,000. Nine of the 10 women experienced amenorrhea. One woman with an "18-week" sized uterus containing a submucous myoma had continued spotting.

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18. Garris PD & Sokol MS: Leuprolide acetate treatment of catamenial pneumothorax. *Fertil Steril*. 1994; 61:173.174.
19. Mathias JR, Clench MH, Abell TL, et al: Effect of leuprolide acetate in treatment of abdominal pain and nausea in premenopausal women with functional bowel disease: a double-blind, placebo-controlled, randomized study. *Dig Dis Sci*. 1998; 43(6):1347-1355.

LUXTURNA (voretigene neparvovec-rzyl)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Luxturna is indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Testing or analysis confirming a genetic diagnosis of biallelic RPE65 gene mutations.

III. CRITERIA FOR INITIAL APPROVAL

Biallelic RPE65 mutation-associated retinal dystrophy
Authorization of 1 month may be granted for treatment of biallelic RPE65 mutation-associated retinal dystrophy when all of the following criteria are met:
A. The member has not received a previous treatment course of Luxturna.
B. The member has viable retinal cells in both eyes as determined by retinal thickness on spectral domain optical coherence tomography, fundus photography, and clinical examination.
C. The member must have either of the following in both eyes:
    1. Visual acuity of 20/60 or worse.
    2. Visual field less than 20 degrees in any meridian.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Luxturna.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Luxturna are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information. Additional coverage requirements can be found in the published clinical trial for this drug. In the open-label, randomized,

controlled phase 3 trial, individuals aged 3 years or older with, in each eye, best corrected visual acuity of 20/60 or worse, or visual field less than 20 degrees in any meridian, or both, with confirmed genetic diagnosis of biallelic RPE65 mutations, sufficient viable retina, and ability to perform standardized multi-luminance mobility testing (MLMT) within the luminance range evaluated, were eligible.

VI. REFERENCES

1. Luxturna [package insert]. Philadelphia, PA: Spark Therapeutics, Inc.; May 2022.
2. Russel S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomized, controlled, open-label phase 3 trial. *Lancet 2017*; 390:849-860.

LYFGENIA (lovotibeglogene autotemcel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Lyfgenia is indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events.

Limitations of Use:
Following treatment with Lyfgenia, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. Lyfgenia has not been studied in patients with more than two α-globin gene deletions.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Molecular or genetic testing results documenting sickle cell disease genotype
B. Chart notes or medical records documenting history of severe vaso-occlusive episodes

III. CRITERIA FOR INITIAL APPROVAL

Sickle Cell Disease
Authorization of one dose total may be granted for sickle cell disease when all of the following criteria are met:
A. Member is 12 years of age or older.
B. Member has a diagnosis of sickle cell disease with one of the following genotypes confirmed by molecular or genetic testing:
    1. β^s/β^s
    2. β^s/β^0
    3. β^s/β^+
C. Member has a documented history of at least 2 severe vaso-occlusive episodes per year during the previous two years (see Appendix for examples).
D. Member is eligible for a hematopoietic stem cell transplant (HSCT) but is unable to find a human leukocyte antigen (HLA)-matched related donor.
E. Member has not received a prior hematopoietic stem cell transplant (HSCT).
F. Member has not received Lyfgenia or any other gene therapy previously.
G. Member does not have more than two α-globin gene deletions.

IV. APPENDIX

Examples of Severe Vaso-Occlusive Events
1. Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
2. Acute chest syndrome
3. Priapism lasting > 2 hours and requiring a visit to a medical facility
4. Splenic sequestration
5. Hepatic sequestration

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Lyfgenia.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. National Institutes of Health.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lyfgenia are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the list of examples of severe vaso-occlusive events can be found in both the clinical trials of Casgevy and Lyfgenia. In addition, the list is further supported by the Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014.

VII. REFERENCES

1. Lyfgenia [package insert]. Somerville, MA: bluebird bio, Inc.; December 2023.
2. Walters JK, Krishnamurti L, Mapara MY, et al. Biologic and clinical efficacy of LentiGlobin for sickle cell disease. NEJM. 2022;386(7):617-628.
3. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. National Institutes of Health. Available at https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed December 13, 2023.

MARGENZA (margetuximab-cmkb)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Margenza is indicated, in combination with chemotherapy, for the treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

B. Compendial Use
Breast cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

Documentation of human epidermal growth factor receptor 2 (HER2) status must be available upon request for all submissions.

III. CRITERIA FOR INITIAL APPROVAL

Breast Cancer
Authorization of 12 months may be granted for treatment of HER2-positive breast cancer with no response to preoperative systemic therapy or HER2-positive recurrent unresectable or metastatic breast cancer, in combination with chemotherapy, for members who have received two or more prior regimens.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen or
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Margenza.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex

c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology
3. NCCN Guideline: Breast cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Margenza are covered in addition to the following:
A. HER2-positive breast cancer, if no response to preoperative systemic therapy
B. HER2-positive breast cancer, recurrent or unresectable disease

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Margenza to treat HER2-positive breast cancer after no response to preoperative systemic therapy or disease that is recurrent unresectable (local or regional) can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Margenza [package insert]. Rockville, MD: MacroGenics, Inc.; May 2023.
2. The NCCN Drugs & Biologics Compendium 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 29, 2023.

MEPSEVII (vestronidase alfa-vjbk)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Mepsevii is indicated in pediatric and adult patients for the treatment of mucopolysaccharidosis VII (MPS VII, Sly syndrome).

Limitations of Use:
The effect of Mepsevii on the central nervous system manifestations of MPS VII has not been determined.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: beta-glucuronidase enzyme assay or genetic testing results supporting diagnosis.
B. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

III. CRITERIA FOR INITIAL APPROVAL

Mucopolysaccharidosis VII (MPS VII, Sly syndrome)
Authorization of 12 months may be granted for treatment of MPS VII (Sly syndrome) when both of the following criteria are met:
A. Diagnosis of MPS VII was confirmed by enzyme assay demonstrating a deficiency of beta-glucuronidase enzyme activity or by genetic testing; AND
B. Member has elevated urinary glycosaminoglycan (uGAG) excretion at a minimum of 2-fold over the mean normal for age at initiation of treatment with the requested medication.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Mepsevii.

2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Mepsevii are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assay or genetic testing prior to initiating Mepsevii to treat MPS VII can be found in the trials cited in the prescribing information. To be included in the trial, the patient must have either had the diagnosis of MPS VII confirmed based on leukocyte or fibroblast glucuronidase enzyme assay, or genetic testing.
Additionally, treatment-naïve patients had to have an elevated urinary glycosaminoglycan (uGAG) excretion at a minimum of 2-fold over normal.

VII. REFERENCES

1. Mepsevii [package insert]. Novato, CA: Ultragenyx Pharmaceutical Inc.; December 2020.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT01856218. An OpenLabel Phase 1/2 Study to Assess the Safety, Efficacy and Dose of Study Drug UX003 Recombinant Human Beta- glucuronidase (rhGUS) Enzyme Replacement Therapy in Patients With Mucopolysaccharidosis Type 7 (MPS 7); January 31, 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT01856218?term=NCT01856218&rank=1.
3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02230566. A Phase 3 Study of UX003 Recombinant Human Betaglucuronidase (rhGUS) Enzyme Replacement Therapy in Patients With Mucopolysaccharidosis Type 7 (MPS 7); February 16, 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT02230566?term=NCT02230566&rank=1.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02432144. A LongTerm Open-Label Treatment and Extension Study of UX003 rhGUS Enzyme Replacement Therapy in Subjects With MPS 7; November 6, 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02432144?term=NCT02432144&rank=1.
5. Harmatz P, et al. A novel Blind Start study design to investigate vestronidase alfa for mucopolysaccharidosis VII, an ultra-rare genetic disease. Mol Genet Metab. 2018 Apr;123(4):488-494.

MIRCERA (methoxy polyethylene glycol-epoetin beta)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Mircera is indicated for the treatment of anemia associated with chronic kidney disease (CKD) in:

- Adult patients on dialysis and adult patients not on dialysis.
- Pediatric patients 5 to 17 years of age on hemodialysis who are converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA.

Limitations of Use:
Mircera is not indicated and is not recommended:

- In the treatment of anemia due to cancer chemotherapy
- As a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia

Mircera has not been shown to improve symptoms, physical functioning, or health-related quality of life.

Note: *Use in members on dialysis is covered under the Medicare Part B dialysis benefit and is excluded from coverage under this policy*

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Note: Requirements regarding hemoglobin level exclude values due to recent transfusion.

Anemia Due to Chronic Kidney Disease (CKD)
Authorization of 12 weeks may be granted for the treatment of anemia due to chronic kidney disease in members not receiving dialysis with a pretreatment hemoglobin of less than 10 g/dL or a hematocrit of less than 30%.

III. CONTINUATION OF THERAPY

Note: Requirements regarding current hemoglobin level exclude values due to recent transfusion.

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 weeks may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Mircera.
B. Mircera is being used to treat anemia due to chronic kidney disease (CKD).
C. Mircera has been effective for treating the diagnosis or condition.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Mircera.

2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Anemia for Chronic Kidney Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Mircera are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Mircera [package insert]. St. Gallen, Switzerland: Vifor (International) Inc.; March 2023.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;Suppl 2:279-335.

MONJUVI (tafasitamab-cxix)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Monjuvi, in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

B. Compendial Uses
B-cell lymphomas
a. Acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma
b. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
c. Follicular lymphoma
d. Monomorphic post-transplant lymphoproliferative disorders (B-cell type)
e. Diffuse large B-cell lymphoma (DLBCL)
f. High-grade B-cell lymphomas (HGBLs)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Chart notes, medical record documentation or claims history supporting previous lines of therapy.

III. CRITERIA FOR INITIAL APPROVAL

B-Cell Lymphomas
Authorization of 12 months may be granted for treatment of relapsed or refractory B-cell lymphomas when all of the following criteria are met:
A. The member has one of the following B-cell lymphoma subtypes:
   i. Acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma (including AIDS-related diffuse large B-cell lymphoma, primary effusion lymphoma, AIDS-related plasmablastic lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma)
   ii. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
   iii. Follicular lymphoma
   iv. Monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type)
   v. Diffuse large B-cell lymphoma (DLBCL) (including DLBCL arising from low grade lymphoma and DLBCL not otherwise specified)
   vi. High-grade B-cell lymphomas (HGBLs)
B. The member is not eligible for an autologous stem cell transplant
C. The requested medication will be used in combination with lenalidomide for up to a maximum of 12 cycles

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section III when there is no evidence of unacceptable toxicity or disease progression while on the current regimen and if the member has completed 12 cycles, the requested drug will be used as monotherapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Monjuvi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-Cell Lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Monjuvi are covered in addition to B-cell lymphomas.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Monjuvi to treat B-Cell Lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Monjuvi [package insert]. Boston, MA: Morphosys US, Inc; June 2023.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 2023.

MYLOTARG (gemtuzumab ozogamicin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Acute Myeloid Leukemia (AML)
1. Newly diagnosed CD33-positive AML in adults and pediatric patients 1 month and older
2. Relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older

B. Compendial Use
Acute promyelocytic leukemia (APL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For AML and APL (initial requests): Testing or analysis confirming tumor is CD33-positive.

III. CRITERIA FOR INITIAL APPROVAL

Acute Myeloid Leukemia (AML)/ Acute Promyelocytic Leukemia (APL)
Authorization of 12 months may be granted for the treatment of AML/APL if the tumor is CD33-positive as confirmed by testing or analysis to identify the CD33 antigen.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all the following criteria are met:
A. The member is currently receiving therapy with Mylotarg.
B. Mylotarg is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
   1. No evidence of unacceptable toxicity while on the current regimen and
   2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Mylotarg.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)

d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Acute myeloid leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Mylotarg are covered in addition to acute promyelocytic leukemia.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Mylotarg to treat acute promyelocytic leukemia can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Mylotarg [package insert]. Philadelphia, PA: Pfizer; August 2021.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed January 5, 2024.

NAGLAZYME (galsulfase)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Naglazyme is indicated for patients with Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome). Naglazyme has been shown to improve walking and stair-climbing capacity.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: N-acetylgalactosamine-4-sulfatase (arylsulfatase B) enzyme assay or genetic testing results supporting diagnosis.
B. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

III. CRITERIA FOR INITIAL APPROVAL

Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)
Authorization of 12 months may be granted for treatment of MPS VI (Maroteaux-Lamy syndrome) when the diagnosis of MPS VI was confirmed by enzyme assay demonstrating a deficiency of N-acetylgalactosamine-4-sulfatase (arylsulfatase B) enzyme activity or by genetic testing.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Naglazyme.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs

e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Naglazyme are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assays or genetic testing prior to starting Naglazyme to treat MPS VI can be found in a guideline by Akyol et al. The diagnosis of MPS VI can be confirmed by one of two ways: confirmation of ASB enzyme activity in cultured fibroblasts or isolated leukocytes of less than 10% of the lower limit of normal or demonstration of two disease-causing mutations.

VII. REFERENCES

1. Naglazyme [package insert]. Novato, CA: BioMarin Pharmaceutical Inc.; December 2019.
2. Akyol, M.U., Alden, T.D., Amartino, H. et al. Recommendations for the management of MPS VI: systematic evidence- and consensus-based guidance. *Orphanet J Rare Dis* 14, 118 (2019).

NEULASTA (pegfilgrastim)
FULPHILA (pegfilgrastim-jmdb)
FYLNETRA (pegfilgrastim-pbbk)
NYVEPRIA (pegfilgrastim- apgf)
STIMUFEND (pegfilgrastim-fpgk)
UDENYCA (pegfilgrastim-cbqv)
ZIEXTENZO (pegfilgrastim-bmez)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

Neulasta

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
   Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
2. Hematopoietic Subsyndrome of Acute Radiation Syndrome
   Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

Fulphila

Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Udenyca

1. Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
2. Hematopoietic Subsyndrome of Acute Radiation Syndrome
   Udenyca is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

Ziextenzo

Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Nyvepria

Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Fylnetra

Patients with Cancer Receiving Myelosuppressive Chemotherapy
Fylnetra is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Stimufend

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Stimufend is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

B. Compendial Uses
1. Stem cell transplantation-related indications
2. Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
3. Hematopoietic Subsyndrome of Acute Radiation Syndrome
4. Hairy cell leukemia, neutropenic fever

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Primary Prophylaxis of Febrile Neutropenia
Documentation of the member's diagnosis and chemotherapeutic regimen.

III. CRITERIA FOR INITIAL APPROVAL

A. Prevention of neutropenia in cancer patients receiving myelosuppressive chemotherapy
Authorization of 6 months may be granted for prevention of febrile neutropenia for members with solid tumors or non-myeloid malignancies when the requested medication will not be administered with weekly chemotherapy regimens and the member will not receive chemotherapy at the same time as they receive radiation therapy.

B. Other indications
Authorization of 6 months may be granted for members with any of the following indications:
1. Stem cell transplantation-related indications
2. Hematopoietic subsyndrome of acute radiation syndrome
3. Hairy cell leukemia with neutropenic fever following chemotherapy

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Neulasta, Fulphila, Fylnetra, Nyvepria, Stimufend, Udenyca, and Ziextenzo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Hematopoietic growth factors
4. NCCN Guideline: Hematopoietic cell transplantation
5. NCCN Guideline: Hairy cell leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Neulasta and its biosimilars are covered in addition to the following:

A. Stem cell transplantation-related indications
B. Prophylaxis for chemotherapy-induced neutropenia in patients with solid tumors
C. Hairy cell leukemia, neutropenic fever

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using pegfilgrastim in mobilization of peripheral blood progenitor cells can be found in a study of patients with non-Hodgkin lymphoma by Russel et al. Patients with non-Hodgkin's lymphoma received one cycle of mobilizing chemotherapy (ifosfamide, carboplatin and etoposide, ICE). Twenty-four hours later they were randomized, double-blind, to receive a single dose of pegfilgrastim 6 mg or 12 mg, or filgrastim 5 mg/kg/day (until the end of leukapheresis). Following leukapheresis (collection phase), patients rested or received one or two 'salvage' cycles of ICE. High-dose BEAM chemotherapy was then given before peripheral blood progenitor cell transplantation. The primary end-point was the patients' mean yield of CD34(+) cells/kg during the collection phase. Ninety patients were randomized and received a study drug; 63% completed the collection phase. The patients' mean (95% CI) CD34(+) cell harvest per leukapheresis was 0.8 (0.5-1.4), 0.8 (0.5-1.6) and 1.2 (0.7-2.0)x10(6) cells/kg for the pegfilgrastim 6 mg, pegfilgrastim 12 mg and filgrastim groups, respectively. Twenty (69%), 17 (59%) and 23 (72%) patients in these three groups achieved the targeted minimum harvest (>/=2 x 10(6) cells/kg). The mean total harvests were 1.7, 1.4 and 2.2 x 10(6) cells/kg, respectively. Post-transplantation, the median days to absolute neutrophil count recovery (>/=0.5 x 10(9)/L) were 12, 11, and 11, respectively. Pegfilgrastim and filgrastim were generally well tolerated.

In a phase 2 study by Fruehauf et al, a single dose of pegfilgrastim 12 mg demonstrated favorable CD34+ cell yields when administered following myeloablative chemotherapy for the mobilization of peripheral blood progenitor cells (PBPC) in patients with multiple myeloma (MM). Patients aged 18 to 65 years (median age, 57 years; range, 40 to 65 years) with stage 2 or 3 MM who were candidates for an autologous transplant were eligible for study enrollment. Most patients had previously received induction therapy with VAD (vincristine, doxorubicin, dexamethasone). Following myeloablative chemotherapy with CAD (cyclophosphamide, doxorubicin, dexamethasone), patients received a single dose of subcutaneous pegfilgrastim 12 mg (n=26) on day 5, approximately 24 hours after chemotherapy completion. In patients with a CD34+ cell count of 20 x 10(6) cells/L or greater (at day 10 or greater), leukapheresis was started between days 15 to 20 and continued until a CD34+ cell count fell to 5 x 10(6)/L or less or a target CD34+ cell harvest of 7.5 x 10(6)/kg was achieved. In patients with a CD34+ cell count between 5 and 20 x 10(6) cells/L (at day 13 or greater) and a platelet count of 30 x 10(9)/L, leukapheresis was continued until the target harvest of 7.5 x 10(6)/kg was achieved. Additional treatment with filgrastim 10 mcg/kg was given if the CD34+ cell count fell by greater than 25% per day starting from day 16 without reaching 20 x 10(6) cells/L. The transplant phase consisted of high-dose melphalan followed by PBPC transfusion. Patients were compared with historical control patients from the same center who received filgrastim (n=52; median age, 60 years; range, 31 to 70 years) matched (1:2) for prior therapy, disease stage, and induction therapy response before mobilization. A CD34+ cell target yield of 7.5 x 10(6) cells/kg or greater (primary endpoint) was achieved in 23 patients (88%; 95% confidence interval, 70% to 98%) who received pegfilgrastim and 41 patients (79%) who received filgrastim (median number of apheresis procedures to target CD34+ cell yield: pegfilgrastim, 2 (range, 1 to 4); filgrastim, 2 (range, 1 to 6)). Three patients who received pegfilgrastim required additional treatment with filgrastim to achieve the target CD34+ cell yield, and all 26 patients received a transplant. The median total CD34+ cell harvests were 9.7 X 10(6) cells/kg (range, 4.9 to 40.5 x 10(6) cells/kg) and 9.95 x 10(6) cells/kg (range, 2.6 to 99.9 X 10(6) cells/kg) for the pegfilgrastim and filgrastim groups, respectively; additionally, the median CD34+ cells per leukapheresis were 4.4 x 10(6) cells/kg (range, 0.9 to 40.5 x 10(6) cells/kg) and 3.4 x 10(6) cells/kg (range, 0.1 to 63.6 x 10(6) cells/kg), respectively. Hematologic recovery following transplant was similar in the pegfilgrastim and filgrastim groups for the median time to leucocyte count of 1 x 10(9)/L or greater (14 days (range, 10 to 21 days) and 14 days (range, 8 to 24 days), respectively) and median time to platelets of 20 x 10(9)/L or greater (11 days (range, 0 to 15 days) and 11 days (range, 0 to 16 days). Adverse events reported with pegfilgrastim use were grade 1 thoracic pain (n=1) and nausea (n=1).

Support for using pegfilgrastim in hematopoietic cell mobilization can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell

transplantation supports the use of pegfilgrastim as treatment for hematopoietic cell mobilization for autologous donors in combination with plerixafor.

Support for using pegfilgrastim for neutropenic fever in a patient being treated for hairy cell leukemia can be found in the National Comprehensive Cancer Network's guideline for hairy cell leukemia. The NCCN Guideline for hairy cell leukemia supports using neutrophil growth factors for patients with neutropenic fever following systemic therapy.

Support for hematopoietic acute radiation syndrome can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors in addition to the prescribing information for Neulasta. The NCCN Guideline for hematopoietic growth factors supports the use of pegfilgrastim in patients with radiation-induced myelosuppression following a radiologic/nuclear incident.

VII. REFERENCES

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NEXVIAZYME (avalglucosidase alfa-ngpt)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Nexviazyme is indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: acid alpha-glucosidase enzyme assay or genetic testing results supporting diagnosis.
B. Continuation requests: chart notes documenting a positive response to therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, walking capacity, respiratory function, muscle strength).

III. CRITERIA FOR INITIAL APPROVAL

Late-onset Pompe disease
Authorization of 12 months may be granted for treatment late-onset Pompe disease when all of the following criteria are met:
A. Member is 1 year of age or older
B. Diagnosis was confirmed by enzyme assay demonstrating a deficiency of acid alpha-glucosidase enzyme activity or by genetic testing

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy (e.g., improvement, stabilization or slowing of disease progression for motor function, walking capacity, respiratory function, or muscle strength).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Nexviazyme.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Nexviazyme are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assays or genetic testing to confirm the diagnosis prior to using Nexviazyme to treat late-onset Pompe disease can be found in the trial cited in the package insert. To be included in the trial, the participant must have either a confirmed acid alpha-glucosidase (GAA) enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations.

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1. Nexviazyme [package insert]. Cambridge, MA: Genzyme Corporation; August 2021.

NOVOSEVEN RT (coagulation factor VIIa [recombinant])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Hemophilia A or hemophilia B with inhibitors
   2. Congenital factor VII deficiency
   3. Glanzmann's thrombasthenia
   4. Acquired hemophilia

B. Compendial Uses
   1. Acquired von Willebrand syndrome
   2. Inhibitors to factor XI
   3. Drug action reversal, anticoagulation
   4. Postoperative hemorrhage, cardiac surgery

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Congenital Factor VII Deficiency
Authorization of 12 months may be granted for treatment of congenital factor VII deficiency.

B. Hemophilia A with Inhibitors
Authorization of 12 months may be granted for treatment of hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

C. Hemophilia B with Inhibitors
Authorization of 12 months may be granted for treatment of hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

D. Glanzmann's Thrombasthenia
Authorization of 12 months may be granted for treatment of Glanzmann's thrombasthenia.

E. Acquired Hemophilia
Authorization of 12 months may be granted for treatment of acquired hemophilia.

F. Acquired von Willebrand Syndrome
Authorization of 12 months may be granted for treatment of acquired von Willebrand syndrome when other therapies failed to control the member's condition (e.g., desmopressin or factor VIII/von Willebrand factor).

G. Inhibitors to Factor XI
Authorization of 12 months may be granted for treatment of inhibitors to factor XI.

H. Anticoagulation Reversal
Authorization of 1 month may be granted for emergency reversal of anticoagulation.

I. Postoperative Hemorrhage following Cardiac Surgery
Authorization of 1 month may be granted for treatment of postoperative hemorrhage following cardiac surgery.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Anticoagulation Reversal
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. Postoperative Hemorrhage following Cardiac Surgery
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

C. All Other Indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. APPENDIX

Appendix: Inhibitors - Bethesda Units (BU)
The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - $\geq$ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Novoseven RT.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. WFH Guidelines for the Management of Hemophilia, 3rd edition.
4. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.
5. World Federation of Hemophilia. Platelet function disorders.
6. Use of recombinant activated factor VII in patients with Glanzmann's thrombasthenia: a review of the literature.
7. Congenital factor XI deficiency: an update.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Novoseven RT are covered in addition to the following:
1. Acquired von Willebrand syndrome
2. Inhibitors to factor XI

3. Drug action reversal, anticoagulation
4. Postoperative hemorrhage, cardiac surgery

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using NovosevenRT to treat acquired von Willebrand syndrome can be found in a study by Tiede et al. Use of recombinant factor VIIa has been reported in AVWS and in von Willebrand disease patients, particularly those who develop alloantibodies against VWF. It is usually administered with a dose of 90 µg/kg (range, 40-150 µg/kg) and for a median of 3 doses (range, 1-54 doses). Treatment is usually effective with responses reported in 96% of patients. Adverse events appear to be uncommon; myocardial infarction was reported in one patient with type 2A von Willebrand disease. The rate of thromboembolic complications is low in hemophilia patients receiving recombinant factor VIIa, but it is currently unknown whether this is holds for patients with AVWS or von Willebrand disease. Caution should be exerted, particularly in elderly patients and those at risk of thromboembolism.

Support for using Novoseven RT to treat inhibitors to factor XI can be found in several articles.
Duga and Salomon state the treatment of factor XI deficiency is difficult because factors influencing bleeding risks are still unknown. The use of lower doses of recombinant activated factor VII in comparison with the doses commonly applied in hemophilia A or B seems promising also when assessed in vitro by thrombin generation test.
Individuals with severe factor XI deficiency who have developed a factor XI inhibitor may not have an increase in factor XI with factor XI replacement products and may require treatment with a bypassing agent such as recombinant activated factor VII (recombinant factor VIIa; rFVIIa). In their review, Roberts et al (2004) state recombinant VIIa has also been used to treat patients with factor XI deficiency either with or without inhibitors to factor XI. Doses of 90 to 120 µg/kg every 2 to 3 hours until bleeding ceases have been found to be effective in this condition, but the optimal dose has not been clearly defined. Some investigators now consider rfVIIa to be the treatment of choice in factor XI deficiency and for inhibitors to factor XI (Roberts 2004).

Support for using Novoseven RT to reverse the effects of anticoagulants can be found in a study by Ingerslev, Vanek and Culic. Activated recombinant factor VII (rFVIIa) was beneficial for patients requiring emergency anticoagulation reversal in a database review of an international, internet-based registry (n=18). Patients who received rFVIIa as rescue treatment for bleeding during or after a surgical or invasive procedure, who had verifiable results and provider consent were included. The anticoagulants utilized, which required reversal included low-molecular-weight heparin (n=6), unfractionated heparin (n=8), coumarin (n=3) and warfarin (n=1). All but 1 patient received a single dose of rFVIIa. The median dose was 87.35 micrograms/kilogram (mcg/kg) (range, 20 to 106 mcg/kg). The primary outcome was cessation of hemorrhage. Cessation of hemorrhage was achieved in 10 patients. A marked reduction in hemorrhage occurred in 5 patients and a considerable slowing of hemorrhage occurred in 3 patients. Neither the severity of initial bleeding nor the dose of rFVIIa seemed to influence efficacy. The need for blood products (packed red blood cells, whole, blood, fresh frozen plasma, cryoprecipitate or platelets) or fluid therapy (crystalloids or colloids) from 24 hours before to 24 hours after treatment significantly improved (p less than 0.001 and p less than 0.05, respectively). No adverse effects were reported and rFVIIa was considered well tolerated. Of the 18 patients, 14 had reported final outcomes: 8 were discharged, 1 stayed in the ICU, and 5 fatalities occurred but were not attributed to rFVIIa.
Ilyas and colleagues completed a retrospective, cohort-controlled database review of elderly patients with intracranial hemorrhage (n=54). Elderly patients treated with warfarin, who presented with a new or developing intracranial bleed and an international normalized ratio (INR) greater than 1.4 received rFVIIa 10 to 100 micrograms/kilogram (mcg/kg) (n=24; age 76.5 +/- 11 years (yr); 50% male). Demographics of the historical controls was similar (n=30; age 76.4 +/- 12.4 yr; 63% male). Patients treated with rFVIIa rapidly achieved INR reduction to 1.3 or less compared with historical controls, 2.4 +/- 1.5 hours (hr) vs 13.7 +/- 15.6 hr, respectively, and INR remained corrected for an average of 12.2 +/- 8.8 hr. Patients treated with rFVIIa required noticeably less plasma for hemostasis compared with historical controls 4 +/- 3 units vs 7.7 +/- 4.4 units, respectively. A dose-response effect in duration of INR correction was observed: 3 hr INR correction with rFVIIa 1.2 milligrams (mg), 13 hr INR correction with 2.4 to 4.8 mg, and 17 hr INR correction for doses greater than 4.8 mg. Most patients received vitamin K 10 mg IV within the first 12 hours of treatment. One patient experienced a myocardial infarction that was temporally related to rFVIIa administration but fully recovered. A study limitation is the retrospective study design.

Support for using Novoseven RT to treat postoperative hemorrhage after cardiac surgery can be found in a meta-analysis by Ponschab et al. In a meta-analysis of 6 clinical trials (2 randomized, 3 propensity matched, and 1 case matched) (n=470), using recombinant activated factor VII (rFVIIa) (18 mcg/kg to 70 mcg/kg given in repeatable doses, and 90 mcg/kg given as a single dose) in post-cardiac surgery patients did not significantly reduce the rate of surgical reexploration (13% vs 42% in the rFVIIa and control groups, respectively) (odds ratio (OR) 0.27; 95% confidence interval (CI) 0.04 to 1.9; p=0.19), and was associated with an increased rate of stroke (4.7% vs 0.9% in the rFVIIa and control groups, respectively) (OR 3.69; 95% CI 1.1 to 12.38; p=0.03). Incidence in overall perioperative vascular events (myocardial infarction, stroke, and DVT) (7.5% vs 5.6% in the rFVIIa and control groups, respectively) (OR 1.84; 95% CI 0.82 to 4.09; p=0.14), and mortality (13% vs 12% in the rFVIIa and control groups, respectively) (OR 1.14; 95% CI 0.65 to 2.01) was not different between the groups. All 6 studies reported reduction in blood loss with rFVIIa; however, due to the different methods of measurement, the results could not be compared between the studies.
Additionally, the use of recombinant activated factor VII (rFVIIa) in patients who bleed after cardiac surgery was effective in a phase II, multicenter, randomized, double-blind, placebo-controlled trial (n=172); however, the incidence of serious adverse events was higher in the rFVIIa group (Gill et al). Patients who were bleeding after cardiac surgery requiring cardiopulmonary bypass (CPB) and needing conventional transfusion therapy or surgical reexploration were randomized to receive placebo (n=68), 40 microgram per kilogram (mcg/kg) rFVIIa (n=35), or 80 mcg/kg rFVIIa (n=69). The study reported that rFVIIa reduced bleeding and patients receiving rFVIIa had significantly fewer reoperations (p=0.03) (placebo, 25%; 40 mcg/kg, 14%; 80 mcg/kg 12%), and less transfusion requirements compared with patients receiving placebo (p=0.01). The primary end point of the study was the number of patients experiencing serious adverse events (SAEs), and the results showed that there were more SAEs (death, acute myocardial infarction, cerebral infarction, pulmonary embolus and other thrombotic events) in the rFVIIa groups than in the placebo group; however, the differences were not statistical significant (placebo, 7%; 40 mcg/kg, 14%; p=0.25; 80 mcg/kg, 12%; p=0.43). There were a total of 14 deaths, with 6% of the placebo group and 10% of the combined rFVIIa dose groups. The major limitation of the study was its small sample size with some of the patients who received rFVIIa were older, were on CPB longer, and received more transfusions before randomization. These factors were strong predictors of the SAEs and mortality and may partially account for its increased number (although statistically insignificant) in rFVIIa-treated patient.

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NPLATE (romiplostim)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Nplate is indicated for the treatment of thrombocytopenia in:
      i. Adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
      ii. Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
   2. Nplate is indicated to increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]).

B. Compendial Uses
   1. Myelodysplastic syndromes, for lower risk disease in patients with severe or refractory thrombocytopenia following disease progression or no response to hypomethylating agents, immunosuppressive therapy
   2. Chemotherapy-induced thrombocytopenia (CIT)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions for immune thrombocytopenia and chemotherapy-induced thrombocytopenia (CIT):
A. For initial requests: pretreatment platelet count
B. For continuation requests: current platelet count

III. CRITERIA FOR INITIAL APPROVAL

A. Immune Thrombocytopenia (ITP)
Authorization of 12 months may be granted for treatment of ITP when both of the following criteria are met:
   1. Untransfused platelet count at any point prior to the initiation of the requested medication is less than $30x10^9$/L OR $30x10^9$/L to $50x10^9$/L with symptomatic bleeding (e.g., significant mucous membrane bleeding, gastrointestinal bleeding or trauma) or risk factors for bleeding (e.g., undergoing a medical or dental procedure where blood loss is anticipated, comorbidities such as peptic ulcer disease and hypertension, mandated anticoagulation therapy, profession [e.g., construction worker] or lifestyle [e.g., plays contact sports] that predisposes patient to trauma).
   2. At least one of the following criteria is met:
      i. The member has previously received treatment with an immunoglobulin for the treatment of ITP.
      ii. The member had an inadequate response to corticosteroids.
      iii. There is a clinical reason to avoid treatment with both immunoglobulins and corticosteroids.
      iv. The member has undergone a splenectomy.

B. Hematopoietic syndrome of acute radiation syndrome (HS-ARS)

Authorization of 1 month may be granted for treatment of hematopoietic syndrome of acute radiation syndrome (acute exposure to myelosuppressive doses of radiation).

C. Myelodysplastic Syndromes

Authorization of 12 months may be granted for treatment of myelodysplastic syndromes with severe or refractory thrombocytopenia when both of the following criteria are met:

1. Member has lower risk disease defined as Revised International Prognostic Scoring System (IPSS-R) (Very Low, Low, Intermediate), International Prognostic Scoring System (IPSS) (Low/Intermediate-1), WHO classification-based Prognostic Scoring System (WPSS) (Very Low, Low, Intermediate).
2. Member has severe or refractory thrombocytopenia following disease progression or no response to hypomethylating agents (such as azacitidine and decitabine), or immunosuppressive therapy.

D. Chemotherapy-induced thrombocytopenia

Authorization of 6 months may be granted for treatment of chemotherapy-induced thrombocytopenia (CIT) when either of the following criteria are met:

1. The platelet count is less than $100x10^9$/L for at least 3-4 weeks following the last chemotherapy administration.
2. Chemotherapy administration has been delayed related to thrombocytopenia.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Immune Thrombocytopenia (ITP)

Authorization may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Nplate.
2. Nplate is being used to treat immune thrombocytopenia (ITP).
3. Either of the following criteria is met:
    i. Authorization of 12 months may be granted for members receiving benefit from therapy. Benefit is defined as any of the following:
        a. Current platelet count less than $50x10^9$/L for whom the current platelet count is sufficient to prevent clinically important bleeding.
        b. Current platelet count of $50x10^9$/L to $200x10^9$/L.
        c. Current platelet count greater than $200x10^9$/L to less than or equal to $400x10^9$/L for whom Nplate dosing will be adjusted to achieve a platelet count sufficient to avoid clinically important bleeding.
    ii. Authorization of 3 months may be granted for members with current platelet count less than $50x10^9$/L for whom the current platelet count is not sufficient to prevent clinically important bleeding and who have not received a maximal Nplate dose for at least 4 weeks.

B. Myelodysplastic Syndromes

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Nplate.
2. Nplate is being used to treat myelodysplastic syndromes (MDS).
3. The member is receiving benefit from therapy. Benefit is defined as any of the following:
    i. Increased platelet counts
    ii. Decreased bleeding events
    iii. Reduced need for platelet transfusions

C. Chemotherapy-Induced Thrombocytopenia

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Nplate.
2. Nplate is being used to treat chemotherapy-induced thrombocytopenia (CIT).
3. The member is receiving benefit from therapy. Benefit is defined as any of the following:
    i. Increased platelet counts
    ii. Decreased bleeding events

iii. Reduced need for platelet transfusions
4. The requested drug is used to maintain dose schedule and intensity of chemotherapy.[10]

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Nplate.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Hematopoietic growth factors
4. NCCN Guideline: Myelodysplastic syndromes
5. American Society of Hematology 2019 guidelines for immune thrombocytopenia.
6. Updated international consensus report on the investigation and management of primary immune thrombocytopenia.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Nplate are covered in addition to the following:
1. Severe or refractory thrombocytopenia in myelodysplastic syndromes
2. Treatment of chemotherapy-induced thrombocytopenia (CIT)

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The safety and efficacy of romiplostim were assessed in 2 double-blind, placebo-controlled clinical studies of 125 adult patients with chronic ITP and in an open-label extension study. In these studies, treatment with romiplostim resulted in dose-dependent increases in platelet counts. After a single subcutaneous dose of 1 to 10 mcg/kg of romiplostim, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2- to 3-week period. The platelet counts were above 50 x 10^9/L for 7 out of 8 patients with chronic ITP who received 6 weekly doses of romiplostim at 1 mcg/kg.

Kuter et al. (2008) assessed the long-term effects of romiplostim in splenectomized and non-splenectomized patients with ITP in 2 parallel trials. A total of 63 splenectomized and 62 non-splenectomized patients with ITP with a mean of 3 platelet counts of 30 x 10^9/L or less were randomly assigned 2:1 to subcutaneous injections of romiplostim (n = 42 in the splenectomized study and n = 41 in the non-splenectomized study) or placebo (n = 21 in both studies) every week for 24 weeks. Doses of romiplostim were adjusted to maintain platelet counts of 50 x 10^9/L to 200 x 10^9/L. The primary objectives were to assess the efficacy of romiplostim as measured by a durable platelet response (platelet count greater than or equal to 50 x 10^9/L during 6 or more of the last 8 weeks of treatment) and treatment safety. The authors reported that a durable platelet response was achieved by 38% (16/42) of the splenectomized patients given romiplostim versus none (0/21) of the placebo patients, and by 61% (25/41) of the non-splenectomized patients given romiplostim versus 0.05% (1/21) given placebo. Eighty-seven percent (20/23) of patients given romiplostim (12/12 splenectomized and 72% (8/11) non-splenectomized patients) reduced or discontinued concurrent therapy compared with 38% (6/16) of those given placebo (1/6 splenectomized and 5/10 non-splenectomized patients). Adverse events were reported to be similar in both groups. Furthermore, no antibodies against romiplostim or thrombopoietin were detected. The authors concluded that romiplostim was well-tolerated and increased and maintained platelet counts in splenectomized and non-splenectomized patients with ITP and that many patients were able to reduce or discontinue other ITP medications.

Following completion of the placebo-controlled studies, 100 patients entered an extension study of long-term romiplostim therapy. The majority of patients maintained platelet counts of 50,000/mcL or greater throughout the study with a median duration of romiplostim treatment of 60 weeks and a maximum duration of 96 weeks.

Support for using Nplate for severe or refractory thrombocytopenia can be found in the American Society of Hematology guidelines for immune thrombocytopenia and the International Consensus Report on the investigation and management of primary immune thrombocytopenia.

Initial treatment for newly-diagnosed adults consists of corticosteroids such as dexamethasone and prednisone and immunoglobulins. Subsequent treatment includes rituximab, eltrombopag, avatrombopag, romiplostim. Subsequent medical treatment options with less robust evidence include azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, mycophenolate mofetil, and vinca alkaloids. Splenectomy is recommended as subsequent treatment.

The goal of treatment is to prevent severe bleeding episodes. According to Provan et al. (2019), treatment should maintain a target platelet level of more than 20-30 x 10^9/L at least for symptomatic patients because risk for major bleeding increases below this level. In the studies cited in the package insert, a durable platelet response was the achievement of a weekly platelet count ≥ 50 × 10^9/L for any 6 of the last 8 weeks of the 24-week treatment period in the absence of rescue medication at any time. A transient platelet response was the achievement of any weekly platelet counts ≥ 50 × 10^9/L for any 4 weeks during the treatment period without a durable platelet response. An overall platelet response was the achievement of either a durable or a transient platelet response.

Support for using Nplate in myelodysplastic syndromes can be found in the National Comprehensive Cancer Network's guideline for myelodysplastic syndrome. The NCCN Guideline supports the use of Nplate for treatment of lower risk disease in patients with severe or refractory thrombocytopenia following disease progression or no response to hypomethylating agents or immunosuppressive therapy. Lower risk myelodysplastic syndrome is defined as Revised International Prognostic Scoring System (IPSS-R) category very low, low, or intermediate.

Support for chemotherapy-induced thrombocytopenia can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors. The NCCN Guideline for hematopoietic growth factors supports the use of Nplate for treatment of chemotherapy-induced thrombocytopenia (CIT). Patients should have platelets less than 100,000/mcL for at least three to four weeks following the last chemotherapy administration and/or following delays in chemotherapy initiation related to thrombocytopenia.

VII. REFERENCES

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5. The NCCN Clinical Practice Guidelines in Oncology® Myelodysplastic Syndrome (Version 1.2023). © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed June 2, 2023.

NUCALA (mepolizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

1. Maintenance Treatment of Severe Asthma
   Nucala is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype.

   Limitations of Use: Not for relief of acute bronchospasm or status asthmaticus

2. Eosinophilic Granulomatosis with Polyangiitis
   Nucala is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

3. Hypereosinophilic Syndrome
   Nucala is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

4. Chronic rhinosinusitis with nasal polyps (CRSwNP)
   Nucala is indicated as add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Asthma:
   1. For initial requests:
      i. Member's chart notes or medical record showing pretreatment blood eosinophil count, dependance on inhaled corticosteroids if applicable.
      ii. Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, documentation of clinical reason to avoid therapy.
   2. For continuation requests: Chart notes or medical record documentation supporting improvement in asthma control.

B. EGPA:
   1. For initial requests:
      i. Member's chart notes or medical record showing pretreatment blood eosinophil count
      ii. Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, documentation of clinical reason to avoid therapy.
   2. For continuation requests: Chart notes or medical record documentation supporting improvement in EGPA control.

C. HES:
   1. For initial requests:
      i. FIP1L1-PDGFRA fusion gene test results

ii. Member's chart notes or medical record showing pretreatment blood eosinophil count
2. For continuation requests: Chart notes or medical record documentation supporting improvement in HES control.

D. CRSwNP:
1. For initial requests:
i. Member's chart notes or medical record showing nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) details (e.g., location, size), or Meltzer Clinical Score or endoscopic nasal polyp score (NPS) (where applicable).
ii. Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.
2. For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

III. CRITERIA FOR INITIAL APPROVAL

A. Eosinophilic asthma

Authorization of 12 months may be granted for treatment of eosinophilic asthma when all of the following criteria are met:
1. Member is 6 years of age or older.
2. Member has a baseline blood eosinophil count (pretreatment with a biologic indicated for asthma) of at least 150 cells per microliter.
3. Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
i. Inhaled corticosteroid
ii. Additional controller (i.e., long acting beta$_2$-agonist, long acting muscarinic antagonist, leukotriene modifier, or sustained release theophylline)
4. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Tezspire, or Xolair).

B. Eosinophilic Granulomatosis with Polyangiitis

Authorization of 12 months may be granted for treatment of eosinophilic granulomatosis with polyangiitis when all of the following criteria are met:
1. Member is 18 years of age or older.
2. Member has a history or the presence of an eosinophil count of more than 1000 cells per microliter or a blood eosinophil level of greater than 10%.
3. Member is currently taking oral corticosteroids, unless contraindicated or not tolerated.

C. Hypereosinophilic Syndrome (HES)

Authorization of 12 months may be granted for treatment of hypereosinophilic syndrome (HES) when all of the following criteria are met:
1. Member is 12 years of age or older.
2. Member does not have either of the following:
i. HES secondary to a non-hematologic cause (e.g., drug hypersensitivity, parasitic helminth infection, [human immunodeficiency virus] HIV infection, non-hematologic malignancy)
ii. FIP1L1-PDGFRA kinase-positive HES
3. Member has a history or presence of a blood eosinophil count of at least 1000 cells per microliter.
4. Member has been on a stable dose of HES therapy (e.g., oral corticosteroid, immunosuppressive, and/or cytotoxic therapy).
5. Member has had HES for at least 6 months.

D. Chronic rhinosinusitis with nasal polyps

Authorization of 6 months may be granted for treatment of chronic rhinosinusitis with nasal polyps when all of the following criteria are met:
1. Member is 18 years of age or older
2. Member has bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal corticosteroid treatment for at least 2 months unless contraindicated or not tolerated; and
3. The member has CRSwNP despite one of the following:
i. Prior sino-nasal surgery

ii. Prior treatment with systemic corticosteroids within the last two years was ineffective, unless contraindicated or not tolerated

4. Member has one of the following:
   i. A bilateral nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) showing polyps reaching below the lower border of the middle turbinate or beyond in each nostril
   ii. Meltzer Clinical Score of 2 or higher in both nostrils
   iii. A total endoscopic nasal polyp score (NPS) of at least 5 with a minimum score of 2 for each nostril
5. Member has symptom of nasal blockage, congestion, or obstruction plus one additional symptom:
   i. Rhinorrhea (anterior/posterior)
   ii. Reduction or loss of smell
   iii. Facial pain or pressure
6. Member will continue to use a daily intranasal corticosteroid while being treated with the requested medication, unless contraindicated or not tolerated.
7. Member will not use Nucala concomitantly with other biologics indicated for chronic rhinosinusitis with nasal polyps (e.g., Dupixent or Xolair).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

A. Eosinophilic Asthma

Authorization of 12 months may be granted for continuation of treatment of eosinophilic asthma when all of the following criteria are met:

1. Member is 6 years of age or older.
2. The member is currently receiving therapy with the requested medication.
3. Nucala is being used to treat an indication enumerated in Section III.
4. The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.
5. Member will not use Nucala concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Tezspire, or Xolair).

B. Eosinophilic granulomatosis with polyangiitis

Authorization of 12 months may be granted for continuation of treatment of eosinophilic granulomatosis with polyangiitis when all of the following criteria are met:

1. Member is 18 years of age or older.
2. The member is currently receiving therapy with the requested medication.
3. The requested medication is being used to treat an indication enumerated in Section III.
4. The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.

C. Hypereosinophilic syndrome (HES)

Authorization of 12 months may be granted for continuation of treatment of HES when all of the following criteria are met:

1. Member is 12 years of age or older.
2. The member is currently receiving therapy with the requested medication.
3. The requested medication is being used to treat an indication enumerated in Section III.
4. The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.

D. Chronic rhinosinusitis with nasal polyps (CRSwNP)

Authorization of 12 months may be granted for continuation of treatment of CRSwNP when all of the following criteria are met:

1. Member is 18 years of age or older.
2. The member is currently receiving therapy with the requested medication.
3. The requested medication is being used to treat an indication enumerated in Section III.
4. The member is receiving benefit from therapy as defined by achieving or maintaining a positive clinical response with the requested medication as evidenced by improvement in signs and symptoms of CRSwNP (e.g., improvement in nasal congestion, nasal polyp size, loss of smell, anterior or posterior

rhinorrhea, sinonasal inflammation, hyposmia and/or facial pressure or pain or reduction in corticosteroid use).
5. Member will not use the requested medication concomitantly with other biologics indicated for chronic rhinosinusitis with nasal polyps (e.g., Dupixent or Xolair).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Nucala.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
3. Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention
4. National Asthma education and Prevention Program Expert Panel 3: Guidelines for the diagnosis and management of asthma
5. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program
6. EAACI biologicals guidelines- recommendations for severe asthma
7. American College of Rheumatology/Vasculitis Foundation Guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis
8. European Position Paper on Rhinosinusitis and Nasal Polyps

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Nucala are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Nucala for allergic asthma can be found in the manufacturer's prescribing information, the Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention guidelines, and the guideline update from the National Asthma Education and Prevention Program. The prescribing information indicates the minimum labeled age for Nucala is six years of age. Nucala should be used in patients whose symptoms are inadequately controlled with inhaled corticosteroids. According to the 2022 update of the GINA Global Strategy for asthma management and prevention, Nucala should be considered as an add-on therapy that is uncontrolled on other medications such as long-acting beta2-agonists, leukotriene receptor antagonists, tiotropium, or inhaled corticosteroids-formoterol maintenance and reliever therapy (MART).

According to the EAACI biologicals guidelines, Nucala should be given as add-on therapy in adults and pediatric patients 12 years and older with uncontrolled severe eosinophilic asthma (blood eosinophil cell counts 300 cells/mcL or more in the past 12 months or 150 cells/mcL or more at initiation) to decrease severe asthma exacerbations (strong recommendation for adults; conditional for pediatric patients), decrease or withdraw corticosteroids (strong recommendation for adults; conditional for pediatric patients), and improve lung function (may be relevant in severe asthma with very low lung function), quality of life, and asthma control (conditional recommendation for all).

Support for using Nucala to treat eosinophilic granulomatosis with polyangiitis can be found in a study by Wechsler et al. In adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA), a randomized trial (N=136) evaluated the addition of mepolizumab versus placebo to stable doses of prednisoLONE or predniSONE with or without additional immunosuppressive therapy. Enrolled participants were at least 18 years of age, had received a diagnosis of relapsing or refractory eosinophilic granulomatosis with polyangiitis at least 6 months previously, and had been taking a stable dose of prednisolone or prednisone (≥7.5 to ≤50.0 mg per day, with or without additional immunosuppressive therapy) for at least 4 weeks before the baseline visit. Eosinophilic granulomatosis with polyangiitis was defined as a history or

presence of asthma, a blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells per cubic millimeter, and the presence of two or more criteria that are typical of eosinophilic granulomatosis with polyangiitis. Nucala was given as a 300mg subcutaneous injection every 4 weeks. In co-primary outcomes, the total accrued weeks of remission over 52 weeks was significantly greater with mepolizumab versus placebo (OR, 5.91; 95% CI, 2.68 to 13.03) and remission at both week 36 and 48 was also significantly improved (32% vs 3%; OR, 16.74; 95% CI, 3.61 to 77.56). Remission for at least 24 weeks was achieved in 28% with Nucala and 3% with placebo; although, in subgroup analyses, the outcome was not significantly different with Nucala versus placebo in patients with an absolute eosinophil count (AEC) less than 150/mm(3) (n=57; 21% vs 7%) but was significantly greater with Nucala in patients with an AEC of 150/mm(3) or greater (n=79; 33% vs 0%). Remission within the first 23 weeks that continued until week 52 (secondary outcome) was also significantly greater with Nucala (19% vs 1%). Remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a 63-point scale) and a prednisoLONE/predniSONE dose of 4 mg/day or less. The time to first relapse was significantly reduced with Nucala versus placebo (HR, 0.32; 95% CI, 0.21 to 0.5); a relapse within the 52-week study period was reported in 56% with Nucala and 82% with placebo (major relapses, 22% vs 35%). The annualized relapse rate was significantly reduced with Nucala (1.14 vs 2.27). Relapses with Nucala and placebo, respectively, were vasculitis (43% and 65%), asthma (37% and 60%), and sinonasal (35% and 51%). Relapse was defined as active vasculitis (BVAS greater than 0), active asthma signs or symptoms and a worsening Asthma Control Questionnaire score, or active nasal or sinus disease with worsening in at least 1 of the sinonasal-symptom items leading to an increase in glucocorticoid dose to more than 4 mg/day of prednisoLONE (or equivalent), initiation of or increase in immunosuppressive therapy, or hospitalization. During weeks 48 through 52, the average prednisoLONE/predniSONE dose was significantly reduced with Nucala versus placebo (OR, 0.2; 95% CI, 0.09 to 0.41), a dosage of 4 mg/day or less was achieved in 44% versus 7%, and discontinuation was achieved in 18% versus 3%. Over the 52-week study period, the mean daily dose was 9.2 mg with mepolizumab and 13.5 mg with placebo. Adverse events were reported in 97% with Nucala and 94% with placebo and included headache (32% vs 18%), nasopharyngitis (18% vs 24%), arthralgia (22% vs 18%), sinusitis (21% vs 16%), and upper respiratory tract infection (21% vs 16%). Serious adverse events were reported in 18% with Nucala and 26% with placebo and included exacerbation or worsening of asthma (3% vs 6%).

Support for using Nucala to treat hypereosinophilic syndrome (HES) can be found in the prescribing information. Nucala compared with placebo significantly reduced HES flares at 32 weeks (28% vs 56%; OR, 0.28; 95% CI, 0.12 to 0.64) in a randomized, double-blind trial (N=108) of adults and adolescents. HES flares were defined as worsening of clinical HES signs and symptoms or increasing eosinophils on at least 2 occasions that resulted in the need to increase oral corticosteroids or increase/add cytotoxic or immunosuppressive therapy. Nucala (300 mg every 4 weeks) versus placebo was also associated with significant reductions in the annualized rate of HES flares (0.5 vs 1.46; RR, 0.34; 95% CI, 0.19 to 0.63), HES flares during week 20 through week 32 (17% vs 35%; OR, 0.33; 95% CI, 0.13 to 0.85), and change from baseline in the median Brief Fatigue Inventory Item 3 score (-0.66 vs +0.32 on a 10-point scale). Patients were 12 years or older (mean age, 46 years) and had HES for at least 6 months (mean duration, 5.55 years). They experienced at least 2 HES flares in the past year (worsening of clinical symptoms or blood eosinophil counts that required an escalation in therapy) and had a blood eosinophil count of 1000 cell/mcL or higher during screening. All patients were on stable HES therapy for at least 4 weeks before randomization, which could include chronic or episodic oral corticosteroids, immunosuppressive, or cytotoxic therapy. Patients with nonhematologic secondary HES or FIP1L1-PDGFR-alpha kinase-positive HES were excluded.

Support for using Nucala to treat chronic rhinosinusitis can be found in the prescribing information. The addition of mepolizumab versus placebo to standard of care significantly improved the change from baseline to week 52 in total endoscopic nasal polyp score (median change, -1 vs 0 on an 8-point scale; difference, -0.73; 95% CI, -1.11 to -0.34) and nasal obstruction visual analog scale (VAS) score (median change, -4.41 vs -0.82 on a 10-point scale; difference, -3.14; 95% CI, -4.09 to -2.18) in the randomized SYNAPSE trial (N=407). The study enrolled adults with recurrent, refractory, severe, bilateral nasal polyp symptoms despite standard of care treatment who were eligible for repeat nasal surgery. Nucala significantly reduced the proportion of patients who required nasal surgery (9% vs 23%) and who required systemic corticosteroids (25% vs 37%). The change in the following scores were also significantly reduced with Nucala: overall symptom VAS score (-4.48 vs -0.9), Sino-Nasal Outcome Test (SNOT)-22 total score (-30 vs -14), composite VAS score (combined nasal obstruction, nasal discharge, throat mucus, and loss of smell scores; -3.96 vs -0.89) and smell VAS score (-0.53 vs 0). Adverse events reported more frequently with Nucala included nasopharyngitis (25% vs 23%), oropharyngeal pain (8% vs 5%), and arthralgia (6% vs 2%). Patients had at least 1 nasal surgery in the past 10 years and required stable maintenance therapy with mometasone furoate intranasal spray for at least 8 weeks before screening.

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6. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, Smith SG, Martin N, Mayer B, Yancey SW, Sousa AR, Chan R, Hopkins C; SYNAPSE study investigators. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021 Apr 16.
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NULIBRY (fosdenopterin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Nulibry is indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: genetic testing results documenting a mutation in the molybdenum cofactor synthesis 1 *(MOCS1)* gene, where applicable.
B. Continuation requests (where applicable):
    1. Genetic testing results documenting a mutation in the molybdenum cofactor synthesis 1 *(MOCS1)* gene.
    2. Chart notes or medical records documenting a benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for encephalopathy and/or seizure activity, improved or normalized uric acid, urinary S-sulfocysteine, and xanthine levels).

III. CRITERIA FOR INITIAL APPROVAL

Molybdenum cofactor deficiency (MoCD) Type A
A. Authorization of 12 months may be granted for treatment of MoCD Type A when the diagnosis was confirmed by genetic testing documenting a mutation in the molybdenum cofactor synthesis 1 *(MOCS1)* gene.

B. Authorization of 3 months may be granted for treatment of MoCD Type A when both of the following criteria are met:
    1. Member has a presumed diagnosis of MoCD Type A and genetic test results are pending.
    2. Member has clinical signs and symptoms associated with MoCD Type A (e.g., encephalopathy, intractable seizures, developmental delay, decreased uric acid levels, elevated urinary S-sulfocysteine and/or xanthine levels).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member meets one of the following criteria:
    1. The member has received less than 12 months of therapy and has genetic testing results documenting a mutation in the molybdenum cofactor synthesis 1 *(MOCS1)* gene.

2. The member has received 12 months of therapy or more and is experiencing benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for encephalopathy and/or seizure activity, improved or normalized uric acid, urinary S-sulfocysteine, and xanthine levels).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Nulibry.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Nulibry are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Nulibry [package insert]. Solana Beach, CA: Sentynl Therapeutics, Inc.; October 2022.
2. Atwal PS, Scaglia F. Molybdenum cofactor deficiency. Mol Genet Metab. 2016;117(1):1-4.
3. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet. 2015; 386: 1955-1963.
4. ClinicalTrials.gov. Study of ORGN001 (formerly ALXN1101) in neonates with molybdenum cofactor deficiency (MOCD) type A. Available at: https://clinicaltrials.gov/study/NCT02629393. Accessed: October 25, 2023.
5. ClinicalTrials.gov. Safety & efficacy study of ORGN001 (formerly ALXN1101) in pediatric patients with MoCD type A currently treated with rcPMP. Available at: https://clinicaltrials.gov/ct2/show/NCT02047461. Accessed: October 25, 2023.

OBIZUR (antihemophilic factor [recombinant], porcine sequence)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Obizur is indicated for the on-demand treatment and control of bleeding episodes in adults with acquired hemophilia A.

Limitations of Use:
A. Safety and efficacy of Obizur has not been established in patients with a baseline anti-porcine factor VIII inhibitor titer of greater than 20 BU.
B. Obizur is not indicated for the treatment of von Willebrand disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Acquired hemophilia A
Authorization of 1 month may be granted for treatment of acquired hemophilia A.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Obizur.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Obizur are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Obizur [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2023.

2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 8, 2023.
3. Gomperts E. Recombinant B domain deleted porcine factor VIII for the treatment of bleeding episodes in adults with acquired hemophilia A. *Expert Review of Hematology*. 2015 Aug;8(4):427-32.

OCREVUS (ocrelizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Ocrevus is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Ocrevus is also indicated for the treatment of primary progressive MS, in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Relapsing Forms of Multiple Sclerosis
Authorization of 12 months may be granted to members who have been diagnosed with a relapsing form of multiple sclerosis (including relapsing-remitting and secondary progressive disease for those who continue to experience relapse).

B. Clinically Isolated Syndrome
Authorization of 12 months may be granted to members for the treatment of clinically isolated syndrome of multiple sclerosis.

C. Primary Progressive Multiple Sclerosis
Authorization of 12 months may be granted to members for the treatment of primary progressive multiple sclerosis.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Ocrevus.
B. Ocrevus is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Ocrevus.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ocrevus are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Ocrevus [package insert]. South San Francisco, CA: Genentech, Inc.; March 2023.

OMVOH (mirikizumab-mrkz)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Omvoh is indicated for the treatment of moderately to severely active ulcerative colitis in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

Ulcerative colitis (UC)
For continuation requests: Chart notes or medical record documentation supporting positive clinical response to therapy or remission.

III. CRITERIA FOR INITIAL APPROVAL

Ulcerative colitis (UC)
Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Ulcerative colitis (UC)
Authorization for 12 months may be granted for treatment of moderately to severely active ulcerative colitis when both of the following criteria are met:

A. The member is currently receiving therapy with Omvoh.
B. The member is receiving benefit from therapy. Benefit is defined as one of the following:
    1. Member has achieved or maintained remission.
    2. Member has achieved or maintained a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:
        i. Stool frequency
        ii. Rectal bleeding
        iii. Urgency of defecation
        iv. C-reactive protein (CRP)
        v. Fecal calprotectin (FC)
        vi. Appearance of the mucosa on endoscopy, computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound
        vii. Improvement on a disease activity scoring tool (e.g., Ulcerative Colitis Endoscopic Index of Severity [UCEIS], Mayo score)

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Omvoh.
2. The available compendium:
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. American College of Gastroenterology Clinical Guideline: Ulcerative Colitis in Adults.
4. American Gastroenterological Association Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Omvoh are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Omvoh [package insert]. Indianapolis, IN: Eli Lilly and Company.; October 2023.
2. Rubin DT, Ananthakrishnan AN, et al. 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol.* 2019;114:384-413.
3. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology.* 2020;158:1450.

ONCASPAR (pegaspargase)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Acute lymphoblastic leukemia (ALL):
1. Oncaspar is indicated as a component of a multi-agent chemotherapeutic regimen for the first line treatment of pediatric and adult patients with ALL.
2. Oncaspar is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with ALL and hypersensitivity to native forms of L-asparaginase.

B. Compendial Uses
1. Extranodal natural killer(NK)/T-cell lymphoma (ENKL)
2. Aggressive NK-cell leukemia (ANKL)
3. Lymphoblastic lymphoma (managed in the same manner as ALL)
4. Acute lymphoblastic leukemia (ALL) as a component of multi-agent chemotherapeutic regimen
5. Pediatric acute lymphoblastic leukemia (ALL) as a component of a multi-agent chemotherapeutic regimen, or as monotherapy for recurrent disease
6. Hepatosplenic T-cell lymphoma
7. Non-Hodgkin’s lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)
Authorization of 12 months may be granted for the treatment of ALL or LL when any of the following criteria are met:
1. The requested medication is used in conjunction with multi-agent chemotherapy
2. The requested medication is used as a single agent for recurrent disease

B. Extranodal NK/T-cell Lymphoma (ENKL) / Aggressive NK-cell Leukemia (ANKL)
Authorization of 12 months may be granted for the treatment of ENKL or ANKL when the requested medication is used in conjunction with multi-agent chemotherapy.

C. Hepatosplenic T-cell Lymphoma
Authorization of 12 months may be granted for the treatment of hepatosplenic T-cell lymphoma as subsequent therapy when the requested medication is used in conjunction with multi-agent chemotherapy.

D. Non-Hodgkin's Lymphoma
Authorization of 12 months may be granted for the treatment of refractory Non-Hodgkin's lymphoma.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen and
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Oncaspar.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: T-cell lymphomas
4. NCCN Guideline: Pediatric acute lymphoblastic leukemia
5. NCCN Guideline: Acute lymphoblastic leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Oncaspar are covered in addition to the following:
1. Extranodal natural killer(NK)/T-cell lymphoma (ENKL)
2. Aggressive NK-cell leukemia (ANKL)
3. Lymphoblastic lymphoma (managed in the same manner as ALL)
4. Acute lymphoblastic leukemia (ALL) as a component of multi-agent chemotherapeutic regimen
5. Pediatric acute lymphoblastic leukemia (ALL) as a component of a multi-agent chemotherapeutic regimen, or as monotherapy for recurrent disease
6. Hepatosplenic T-cell lymphoma
7. Non-Hodgkin's lymphoma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Oncaspar to treat the below listed indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).
1. Extranodal natural killer(NK)/T-cell lymphoma (ENKL)
2. Aggressive NK-cell leukemia (ANKL)
3. Lymphoblastic lymphoma (managed in the same manner as ALL)
a. Acute lymphoblastic leukemia (ALL) as a component of multi-agent chemotherapeutic regimen
4. Pediatric acute lymphoblastic leukemia (ALL) as a component of a multi-agent chemotherapeutic regimen, or as monotherapy for recurrent disease
5. Hepatosplenic T-cell lymphoma

Support for using Oncaspar to treat non-Hodgkin's lymphoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Oncaspar has demonstrated some activity in patients with refractory non-Hodgkin's lymphoma.

VI. REFERENCES

1. Oncaspar [package insert]. Boston, MA: Servier Pharmaceuticals LLC; December 2022.
2. The NCCN Drugs & Biologics Compendium® ©2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed May 31, 2023.
3. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com [available with subscription]. Accessed May 31, 2023.

ONIVYDE (irinotecan liposome injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
   1. Onivyde, is indicated, in combination with oxaliplatin, fluorouracil, and leucovorin for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma.
   2. Onivyde is indicated, in combination with fluorouracil and leucovorin, for the treatment of adult patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

   Limitation of Use: Onivyde is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

B. Compendial Uses
   1. Locally advanced, recurrent, or metastatic adenocarcinoma of the pancreas
   2. Ampullary Adenocarcinoma
   3. Hepatobiliary Cancers
      a. Intrahepatic Cholangiocarcinoma
      b. Extrahepatic Cholangiocarcinoma
      c. Gallbladder Cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Adenocarcinoma of the Pancreas
1. Authorization of 12 months may be granted for the first-line therapy or as induction therapy followed by chemoradiation for locally advanced or metastatic pancreatic adenocarcinoma when used in combination with oxaliplatin, fluorouracil, and leucovorin.
2. Authorization of 12 months may be granted for treatment of locally advanced, recurrent, or metastatic adenocarcinoma of the pancreas when used in combination with fluorouracil and leucovorin.

Ampullary Adenocarcinoma
Authorization of 12 months may be granted for subsequent treatment of ampullary adenocarcinoma when used in combination with fluorouracil and leucovorin.

Hepatobiliary Cancers
Authorization of 12 months may be granted for subsequent treatment of unresectable or resected gross residual (R2), or metastatic intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer when used in combination with fluorouracil and leucovorin.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Onivyde
2. Onivyde is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Onivyde.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Ampullary Adenocarcinoma
4. NCCN Guideline: Pancreatic adenocarcinoma
5. NCCN Guideline: Hepatobiliary cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Onivyde are covered in addition to the following:

1. Ampullary adenocarcinoma
2. Locally advanced, recurrent, or metastatic adenocarcinoma of the pancreas
3. Hepatobiliary cancers

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Onivyde to treat locally advanced, recurrent or metastatic ampullary adenocarcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Onivyde as subsequent treatment of unresectable or resected gross residual (R2) or metastatic hepatobiliary cancers can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Onivyde [package insert]. Cambridge, MA: Ipsen Biopharmaceuticals, Inc; February 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 22, 2024.

ONPATTRO (patisiran)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Onpattro is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial Requests:
   1. Testing or analysis confirming a mutation of the TTR gene
   2. Documentation confirming the member demonstrates signs and symptoms of polyneuropathy (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy)
B. Continuation Requests: Chart notes or medical record documentation confirming the clinical benefit from Onpattro

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a neurologist, geneticist, or physician specializing in the treatment of amyloidosis.

IV. CRITERIA FOR INITIAL APPROVAL

Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis
Authorization of 12 months may be granted for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (also called transthyretin-type familial amyloid polyneuropathy [ATTR-FAP]) when all of the following criteria are met:
A. The diagnosis is confirmed by detection of a mutation of the TTR gene.
B. Member exhibits clinical manifestations of ATTR-FAP (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy).
C. The requested medication will not be used in combination with inotersen (Tegsedi), tafamidis (Vyndaqel, Vyndamax) or vutrisiran (Amvuttra).

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving treatment with Onpattro.

B. Onpattro is being used for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis.
C. There is a clinical benefit from Onpattro therapy.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Onpattro.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Guideline of transthyretin-related hereditary amyloidosis for clinicians
4. Familial transthyretin amyloidosis. In: GeneReviews

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Onpattro are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the above initial criteria can be found in a guideline from Ando and colleagues and a Gene Reviews chapter discussing hereditary transthyretin amyloidosis. The diagnosis of ATTR should be suspected in patients with progressive sensorimotor and/or autonomic neuropathy. The diagnosis of hereditary ATTR is established when characteristic clinical features are present, a biopsy showing amyloid deposits that bind to anti-TTR antibodies, and identification of mutations of the TTR gene.
The treatment for peripheral and autonomic neuropathy is orthotopic liver transplantation, TTR tetramer stabilizers and gene-silencing therapies. Liver transplantation provides a wild type gene expressing normal TTR in the liver. Successful liver transplantation results in the disappearance of the variant TTR protein and thus halts the progression of peripheral and/or autonomic neuropathy.

VIII. REFERENCES

1. Onpattro [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; January 2023.
2. Adams, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5; 379(1):11-21.
3. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L, Planté-Bordeneuve V, Rapezzi C, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013; 8:31.
4. Sekijima Y, Yoshida K, Tokuda T, Ikeda S. Familial transthyretin amyloidosis. In: GeneReviews. Seattle (WA): University of Washington, Seattle. 1993-2017. https://www.ncbi.nlm.nih.gov/books/NBK1194/. Accessed March 15, 2023.

OPDIVO (nivolumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Unresectable or Metastatic Melanoma
   Opdivo (nivolumab), as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.

2. Adjuvant Treatment of Melanoma
   Opdivo is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected stage IIB, stage IIC, stage III, or stage IV.

3. Metastatic Non-Small Cell Lung Cancer
   Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

   Opdivo, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

   Opdivo is indicated for the treatment of adult patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.

4. Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer
   Opdivo, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

5. Malignant Pleural Mesothelioma
   Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

6. Advanced Renal Cell Carcinoma
   a. Opdivo as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
   b. Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of patients with intermediate or poor risk advanced RCC.
   c. Opdivo, in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced RCC.

7. Classical Hodgkin Lymphoma
   Opdivo is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:
   a. Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
   b. Three or more lines of systemic therapy that includes autologous HSCT.

8. Squamous Cell Carcinoma of the Head and Neck

Opdivo (nivolumab) is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

9. Urothelial Carcinoma
   a. Opdivo is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
   b. Opdivo is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
      i. Have disease progression during or following platinum-containing chemotherapy
      ii. Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

10. Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer
    Opdivo, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

11. Hepatocellular Carcinoma
    Opdivo, in combination with ipilimumab, is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib.

12. Esophageal Cancer
    a. Opdivo is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy (CRT).
    b. Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
    c. Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
    d. Opdivo is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

13. Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
    Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

B. <u>Compendial Uses</u>
   1. Cutaneous melanoma
   2. Non-small cell lung cancer
   3. Colorectal cancer, including appendiceal adenocarcinoma
   4. Urothelial carcinoma
      a. Bladder cancer
      b. Primary carcinoma of the urethra
      c. Upper genitourinary tract tumors
      d. Urothelial carcinoma of the prostate
   5. Renal cell carcinoma
   6. Head and neck cancers
      a. Very advanced head and neck cancer
      b. Mucosal melanoma
      c. Cancer of the nasopharynx
   7. Classical Hodgkin lymphoma
   8. Hepatocellular carcinoma
   9. Uveal melanoma
   10. Anal carcinoma

11. Merkel cell carcinoma
12. Central nervous system (CNS) brain metastases
13. Pleural mesothelioma
14. Peritoneal mesothelioma
15. Gestational trophoblastic neoplasia
16. Diffuse large B-cell lymphoma
    a. Primary mediastinal large B-cell lymphoma
    b. Histologic (Richter's) transformation to diffuse large B-cell lymphoma
17. Small bowel adenocarcinoma
18. Ampullary adenocarcinoma
19. Extranodal NK/T-cell lymphoma
20. Neuroendocrine tumors
    a. Poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma
    b. Well-differentiated grade 3 neuroendocrine tumors
21. Endometrial carcinoma
22. Vulvar Cancer
23. Gastric cancer
24. Esophageal and esophagogastric junction cancers
25. Biliary tract cancers
    a. Gallbladder cancer
    b. Intrahepatic cholangiocarcinoma
    c. Extrahepatic cholangiocarcinoma
26. Cervical cancer
27. Small cell lung cancer
28. Kaposi Sarcoma
29. Bone Cancer
30. Pediatric Diffuse High-Grade Gliomas
31. Pancreatic adenocarcinoma
32. Soft Tissue Sarcoma
    a. Extremity/body wall sarcoma
    b. Head/neck sarcoma
    c. Retroperitoneal/intra-abdominal sarcoma
    d. Rhabdomyosarcoma
    e. Angiosarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
1. Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor status, where applicable.
2. Documentation of the presence of EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous melanoma

Authorization of 12 months may be granted for treatment of cutaneous melanoma in either of the following settings:
1. For treatment of locally recurrent, unresectable or metastatic disease.
2. The requested medication will be used as adjuvant treatment of stage III or IV disease following complete resection or no evidence of disease.
3. The requested medication will be used as a single agent as adjuvant treatment of stage IIB and IIC disease following complete resection.

B. Non-small cell lung cancer

1. Authorization of 12 months may be granted for treatment of recurrent, advanced, or metastatic NSCLC when either of the following conditions is met:
   a. There are no EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue) and the requested medication will be used in a regimen containing ipilimumab.
   b. The requested medication will be used as a single agent as subsequent therapy.
2. Authorization of 3 months (for up to 3 cycles total) may be granted for neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC) in combination with platinum-doublet chemotherapy.

C. Colorectal cancer

Authorization of 12 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, when member has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.

D. Urothelial carcinoma

Authorization of 12 months may be granted for treatment of urothelial carcinoma, including bladder cancer, upper genitourinary tract tumors, urothelial carcinoma of the prostate, and primary carcinoma of the urethra.

E. Renal cell carcinoma

Authorization of 12 months may be granted for treatment of renal cell carcinoma for relapsed, advanced or stage IV disease.

F. Head and neck cancers

Authorization of 12 months may be granted for treatment of head and neck cancers, including very advanced head and neck cancer, mucosal melanoma, and cancer of the nasopharynx.

G. Classical Hodgkin lymphoma (cHL)

Authorization of 12 months may be granted for the treatment of classical Hodgkin lymphoma.

H. Hepatocellular carcinoma

Authorization of 12 months may be granted for treatment of hepatocellular carcinoma.

I. Uveal melanoma

Authorization of 12 months may be granted for treatment of uveal melanoma.

J. Anal carcinoma

Authorization of 12 months may be granted for treatment of anal carcinoma.

K. Merkel cell carcinoma

Authorization of 12 months may be granted for treatment of Merkel cell carcinoma.

L. CNS brain metastases

Authorization of 12 months may be granted for treatment of CNS brain metastases in patients with melanoma or NSCLC.

M. Pleural or peritoneal mesothelioma

Authorization of 12 months may be granted for treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma, in either of the following settings:

1. The requested medication will be used as first-line therapy in combination with ipilimumab.
2. The requested medication will be used as subsequent therapy as a single agent or in combination with ipilimumab.

N. Gestational Trophoblastic Neoplasia

Authorization of 12 months may be granted for treatment of gestational trophoblastic neoplasia.

O. Diffuse large B-cell lymphoma

Authorization of 12 months may be granted for treatment of either of the following:
1. Primary mediastinal large B-cell lymphoma
2. Histologic (Richter's) transformation to diffuse large B-cell lymphoma.

P. Esophageal and esophagogastric junction carcinoma
1. Authorization of 12 months may be granted for treatment of esophageal and esophagogastric junction carcinoma in members who are not surgical candidates or have unresectable, recurrent, or metastatic disease when the requested medication will be used in combination with ipilimumab or chemotherapy, or will be used as subsequent therapy.
2. Authorization of 12 months may be granted for adjuvant treatment of completely resected esophageal or esophagogastric junction cancer with residual pathologic disease.
3. Authorization of 12 months may be granted as a single agent or in combination with ipilimumab for neoadjuvant or perioperative treatment of esophageal or esophagogastric junction adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.

Q. Small bowel adenocarcinoma
Authorization of 12 months may be granted for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high (MSI-H) or mismatch repair deficient tumors (dMMR), as a single agent or in combination with ipilimumab.

R. Ampullary adenocarcinoma
Authorization of 12 months may be granted for treatment of progressive, unresectable, or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma in combination with ipilimumab.

S. Extranodal NK/T-cell lymphoma
Authorization of 12 months may be granted for treatment of extranodal NK/T-cell lymphoma.

T. Neuroendocrine tumors
Authorization of 12 months may be granted for treatment of neuroendocrine tumors, including poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma and well-differentiated grade 3 neuroendocrine tumors, in combination with ipilimumab.

U. Endometrial carcinoma
Authorization of 12 months may be granted for treatment of endometrial carcinoma with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.

V. Vulvar cancer
Authorization of 12 months may be granted for treatment of human papillomavirus (HPV)-related vulvar cancer.

W. Gastric cancer
Authorization of 12 months may be granted for treatment of gastric cancer in any of the following settings:
1. When the requested medication is being used in members who are not surgical candidates or have unresectable, recurrent, or metastatic disease, when the requested medication will be used in combination with ipilimumab or chemotherapy.
2. When the requested medication will be used as a single agent or in combination with ipilimumab for neoadjuvant or perioperative treatment of gastric adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.

X. Biliary tract cancers
Authorization of 12 months may be granted for treatment of biliary tract cancers, including gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma.

Y. Cervical cancer
Authorization of 12 months may be granted for subsequent treatment of recurrent, or metastatic cervical cancer.

Z. Small cell lung cancer
Authorization of 12 months may be granted for subsequent treatment of relapsed or progressive small cell lung cancer.

AA. Kaposi Sarcoma
Authorization of 12 months may be granted in combination with ipilimumab for subsequent treatment of relapsed/refractory classic Kaposi Sarcoma.

BB. Bone Cancer
Authorization of 12 months may be granted in combination with ipilimumab for unresectable or metastatic bone cancer with tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors.

CC. Pediatric Diffuse High-Grade Gliomas
Authorization of 12 months may be granted for hypermutant tumor pediatric diffuse high-grade glioma as adjuvant treatment or for recurrent or progressive disease.

DD. Soft Tissue Sarcoma
Authorization of 12 months may be granted for treatment of soft tissue sarcoma in the following settings:
1. The requested medication will be used as a single agent or in combination with ipilimumab for treatment of extremity/body wall sarcomas, head/neck sarcomas and retroperitoneal/intra-abdominal sarcomas and rhabdomyosarcoma.
2. The requested medication will be used in combination with ipilimumab for the treatment of angiosarcoma.

EE. Pancreatic Adenocarcinoma
Authorization of 12 months may be granted in combination with ipilimumab for treatment of locally advanced, metastatic, or recurrent pancreatic adenocarcinoma with tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors.

IV. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma
Authorization for 12 months total therapy may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used as adjuvant treatment for a member with melanoma.
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen AND
    b. No evidence of disease recurrence while on the current regimen.

B. Non-small cell lung cancer or pleural mesothelioma
1. Authorization for 12 months may be granted (up to 24 months total when used in combination with ipilimumab) for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
    a. The member is currently receiving therapy with the requested medication.
    b. The requested medication is being used to treat non-small cell lung cancer or pleural, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes.
    c. The member is receiving benefit from therapy. Benefit is defined as:
        i. No evidence of unacceptable toxicity while on the current regimen AND
        ii. No evidence of disease progression while on the current regimen.
2. Neoadjuvant treatment of NSCLC will be approved for a total of 3 months of therapy.

C. Renal cell carcinoma
Authorization for 12 months may be granted (up to 24 months total when used in combination with cabozantinib) for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat renal cell carcinoma.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen AND
   b. No evidence of disease progression while on the current regimen.

D. Gastric cancer, esophageal cancer, and esophagogastric junction carcinoma

Authorization of 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen AND
   b. No evidence of disease progression while on the current regimen.

Therapy durations will be limited to the following:
1. Esophageal squamous cell carcinoma in combination with ipilimumab or chemotherapy for up to 24 months
2. Unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma as a single agent until disease progression or unacceptable toxicity
3. Adjuvant treatment of resected esophageal or esophagogastric junction cancer as a single agent for up to 12 months
4. Gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma in combination with chemotherapy for up to 24 months

E. All other indications

Authorization for 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat any other diagnosis or condition enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen AND
   b. No evidence of disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Opdivo.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Hodgkin lymphoma
4. NCCN Guideline: Small cell lung cancer
5. NCCN Guideline: Vulvar cancer
6. NCCN Guideline: Cervical cancer
7. NCCN Guideline: Gestational trophoblastic neoplasia
8. NCCN Guideline: Small bowel adenocarcinoma
9. NCCN Guideline: Peritoneal mesothelioma
10. NCCN Guideline: Pleural mesothelioma
11. NCCN Guideline: T-cell lymphomas
12. NCCN Guideline: Pediatric Hodgkin lymphoma
13. NCCN Guideline: Cutaneous melanoma
14. NCCN Guideline: Merkel cell carcinoma
15. NCCN Guideline: Non-small cell lung cancer
16. NCCN Guideline: Hepatocellular carcinoma

17. NCCN Guideline: Anal carcinoma
18. NCCN Guideline: Uveal melanoma
19. NCCN Guideline: Gastric cancer
20. NCCN Guideline: Esophageal and esophagogastric junction
21. NCCN Guideline: Central nervous system cancers
22. NCCN Guideline: Biliary tract cancers
23. NCCN Guideline: Ampullary adenocarcinoma
24. NCCN Guideline: Bladder cancer
25. NCCN Guideline: Colon cancer
26. NCCN Guideline: Rectal cancer
27. NCCN Guideline: Head and neck cancers
28. NCCN Guideline: Kidney cancer
29. NCCN Guideline: Pediatric central nervous system cancers
30. NCCN Guideline: Pancreatic adenocarcinoma
31. NCCN Guideline: Chronic lymphocytic leukemia/Small lymphocytic lymphoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Opdivo and are included in addition to the following:

A. Cutaneous melanoma
B. Non-small cell lung cancer
C. Colorectal cancer, including appendiceal adenocarcinoma
D. Urothelial carcinoma
E. Renal cell carcinoma
F. Head and neck cancers
G. Classical Hodgkin lymphoma
H. Hepatocellular carcinoma
I. Uveal melanoma
J. Anal carcinoma
K. Merkel cell carcinoma
L. Central nervous system (CNS) brain metastases
M. Pleural mesothelioma
N. Peritoneal mesothelioma
O. Gestational trophoblastic neoplasia
P. Diffuse large B-cell lymphoma
Q. Small bowel adenocarcinoma
R. Ampullary adenocarcinoma
S. Extranodal natural killer (NK)/T-cell lymphoma
T. Neuroendocrine tumors
U. Endometrial carcinoma
V. Vulvar carcinoma
W. Gastric cancer
X. Esophageal and esophagogastric junction cancers
Y. Cervical cancer
Z. Small cell lung cancer
AA. Kaposi sarcoma
BB. Bone cancer
CC. Pediatric diffuse high-grade gliomas
DD. Biliary tract cancers
EE. Soft tissue sarcoma
FF. Pancreatic adenocarcinoma
GG. Histologic (Richter's) transformation to diffuse large B-cell lymphoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using Opdivo to treat the indications in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; October 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed December 8, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed December 8, 2023

OPDUALAG (nivolumab and relatlimab-rmbw)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Opdualag is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Melanoma
Authorization of 6 months may be granted for treatment of adult members and children 12 years of age and older weighing at least 40 kg, with unresectable or metastatic melanoma.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Opdualag.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Cutaneous melanoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Opdualag are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Opdualag [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; March 2022.

ORENCIA (abatacept)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Treatment of moderately to severely active rheumatoid arthritis (RA) in adults
   2. Treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older
   3. Treatment of active psoriatic arthritis (PsA) in patients 2 years of age and older
   4. Prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor

   Limitation of use: Concomitant use of Orencia with other potent immunosuppressants [e.g., biologic disease-modifying antirheumatic drugs (bDMARDs), Janus kinase (JAK) inhibitors] is not recommended.

B. Compendial Uses
   1. Methotrexate-naive, early rheumatoid arthritis patients with poor prognostic factors
   2. Giant cell arteritis
   3. Chronic graft versus host disease
   4. Immune checkpoint inhibitor-related toxicity
   5. Oligoarticular juvenile idiopathic arthritis

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Rheumatoid arthritis (RA), articular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and giant cell arteritis
   For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

B. Chronic graft versus host disease
   For initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.
   For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

C. Immune checkpoint inhibitor-related toxicity
   For initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Rheumatoid arthritis (RA)
Authorization of 12 months may be granted for treatment of active rheumatoid arthritis.

B. Articular juvenile idiopathic arthritis (JIA)
Authorization of 12 months may be granted for treatment of active articular juvenile idiopathic arthritis.

C. Psoriatic arthritis (PsA)
Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

D. Prophylaxis of acute graft versus host disease
Authorization of 1 month may be granted for prophylaxis of acute graft versus host disease when both of the following criteria are met:
1. Member is undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.
2. The requested medication will be used in combination with a calcineurin inhibitor (e.g., cyclosporine, tacrolimus) and methotrexate.

E. Giant cell arteritis
Authorization of 12 months may be granted for treatment of giant cell arteritis.

F. Chronic graft versus host disease
Authorization of 12 months may be granted for treatment of chronic graft versus host disease when either of the following criteria is met:
1. Member has experienced an inadequate response to systemic corticosteroids.
2. Member has an intolerance or contraindication to corticosteroids.

G. Immune checkpoint inhibitor-related toxicity
Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when the member has myocarditis and has not responded to systemic corticosteroids.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Prophylaxis of acute graft versus host disease and immune checkpoint inhibitor-related toxicity
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. All other indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Orencia.
2. Orencia is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Orencia.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update
4. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.
5. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.

6. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features
7. 2013 Update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis.
8. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.
9. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis.
10. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis.
11. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis.
12. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Orencia are covered in addition to the following:

1. Methotrexate-naive, early rheumatoid arthritis patients with poor prognostic factors
2. Giant cell arteritis
3. Chronic graft versus host disease
4. Immune checkpoint inhibitor-related toxicity
5. Oligoarticular juvenile idiopathic arthritis

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Orencia to treat methotrexate-naïve, early rheumatoid arthritis patients with poor prognostic factors can be found in a study by Westhovens et al. Abatacept plus methotrexate compared with placebo plus methotrexate significantly improved the rate of remission at 1 year (41.4% vs 23.3%) and the extent of structural damage (mean change from baseline in Genant-modified Sharp scoring system total score [TS], 0.63 vs 1.06), in a randomized trial (N=509) of methotrexate-naïve patients with rheumatoid arthritis. Remission was defined as a disease activity score in 28 joints (DAS28; C-reactive protein [CRP]) of less than 2.6. At 1 year, abatacept plus methotrexate compared with methotrexate alone was associated with significant differences in mean change from baseline to 1 year in DAS28 (CRP)(-3.22 vs -2.49), American College of Rheumatology 50% improvement (ACR50; 57.4% vs 42.3%), ACR70 (42.6% vs 27.3%), ACR90 (16.4% vs 6.7%), and major clinical response (ACR70 for at least 6 months, 27.3% vs 11.9%). At 1 year, abatacept plus methotrexate was also associated with a significant difference in Genant-modified Sharp erosion score (mean change from baseline, 0.5 vs 0.89) but not joint-space narrowing score (mean change from baseline, 0.13 vs 0.17), and there was no significant difference in the proportion of patients with no radiographic progression (TS 0 or less; 61.2% vs 52.9%). A health assessment questionnaire disability index (HAQ-DI) change from baseline of 0.3 or more units was achieved by significantly more patients with abatacept and methotrexate (71.9% vs 62.1%). Adverse events were reported in 84.8% with abatacept plus methotrexate versus 83.4% with placebo plus methotrexate, with infections being the most common (51.6% vs 54.9%); serious adverse events were reported in 7.8% and 7.9%, respectively. Adults enrolled in the study had rheumatoid arthritis for 2 years or less, at least 12 tender and 10 swollen joints, CRP of 0.45 mg/dL or higher, rheumatoid factor of anti-cyclic citrullinated protein type 2 positivity, and radiographic evidence of bone erosion of hands/wrists/feet. Abatacept 10 mg/kg IV infusion was given on days 1, 15, and 29, then every 4 weeks. Methotrexate 7.5 mg/week was increased to 15 mg/week at week 4, then to 20 mg/week at week 8. Oral corticosteroids (10 mg predniSONE equivalent or less daily) and up to 2 corticosteroid pulses (more than 10 mg predniSONE or equivalent orally for at least 3 consecutive days or injectable corticosteroids) were permitted during any 6-month period. A non-biological disease modifying antirheumatic drug (DMARD) was allowed after 6 months.

Support for using Orencia to treat giant cell arteritis can be found in a study by Langford et al. During a randomized, double-blind trial (N=41), the relapse-free survival rate at 1 year was significant in patients who received abatacept (48%) compared with patients who received placebo (31%), and the median duration of remission was significantly longer (9.9 vs 3.9 months, respectively). Patients with newly diagnosed or relapsing giant cell arteritis were treated with abatacept 10 mg/kg (500 mg for body weight less 60 kg, 750 mg

for 60 to 100 kg, and 1000 mg for greater than 100 kg) IV infusion on days 1, 15, 29 and week 8, in combination with oral predniSONE 40 to 60 mg/day. Those who achieved remission after 12 weeks of treatment were randomized to continue abatacept every 4 weeks or switch to placebo, in combination with oral predniSONE 20 mg/day, which was tapered after randomization so that all patients discontinued predniSONE at week 28. Seven of the 41 randomized patients withdrew prior to week 64, and a subset analysis performed on the remaining 34 patients at week 64 demonstrated a significant relapse-free survival rate at 1 year for abatacept (52.9%) vs placebo (23.5%). There was no difference in the severity or frequency of adverse events between treatment groups.

Support for using Orencia to treat chronic graft-versus-host disease can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline supports the use of Orencia for chronic graft-versus-host disease as an additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using Orencia to treat immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline supports the use of Orencia as a further intervention for the management of myocarditis if no improvement within 24 to 48 hours of starting high-dose methylprednisolone.

Support for using Orencia to treat oligoarticular juvenile idiopathic arthritis can be found in the 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. In children with oligoarticular JIA, give biologic disease-modifying antirheumatic drugs (DMARDs). This approach is preferred instead of combining or switching conventional synthetic DMARDs due to reported greater probability of achieving rapid and sustained response.

VII. REFERENCES

1. Orencia [package insert]. Princeton, NJ: Bristol-Myers Squibb; October 2023.
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OXLUMO (lumasiran)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Oxlumo is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Molecular genetic test results demonstrating a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene or liver enzyme analysis results demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity.
B. Chart notes or medical records demonstrating a benefit from therapy (for continuation requests).

III. CRITERIA FOR INITIAL APPROVAL

Primary hyperoxaluria type 1
Authorization of 12 months may be granted for the treatment of primary hyperoxaluria type 1 (PH1) when the diagnosis is confirmed by either of the following:
A. Molecular genetic test results showing a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene.
B. Liver enzyme analysis results demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Oxlumo.
B. Oxlumo is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., decrease or normalization of urinary and/or plasma oxalate levels, improvement in kidney function).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Oxlumo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex

c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. The primary hyperoxalurias: an algorithm for diagnosis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Oxlumo are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the diagnostic criteria for primary hyperoxaluria type 1 can be found in a review article by Cochat and Rumsby. A definitive diagnosis of primary hyperoxaluria in a patient with clinical signs and symptoms requires genetic testing to detect a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene. In some cases, the phenotype is typical of primary hyperoxaluria, but no mutation is detected, either because the mutation lies in a promoter or other regulatory sequence or because some other, as yet undefined, metabolic defect is present (i.e., "uncategorized" primary hyperoxaluria). In such cases, a liver biopsy can be performed to test for levels of AGT and GRHPR activity; if the results are negative, primary hyperoxaluria types 1 and 2 can be ruled out.

VII. REFERENCES

1. Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; September 2023.
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OZURDEX (dexamethasone implant)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
   1. Retinal Vein Occlusion
      Ozurdex is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

   2. Posterior Segment Uveitis
      Ozurdex is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

   3. Diabetic Macular Edema
      Ozurdex is indicated for the treatment of diabetic macular edema.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Retinal Vein Occlusion
Authorization of 12 months may be granted for treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) when all of the following criteria are met:
1. The member does not have an ocular or periocular infection
2. The member does not have glaucoma with a cup-to-disc ratio of greater than 0.8
3. The member does not have a torn or ruptured posterior lens capsule

Posterior Segment Uveitis
Authorization of 12 months may be granted for treatment of non-infectious uveitis affecting the posterior segment of the eye when all of the following criteria are met:
1. The member does not have an ocular or periocular infection
2. The member does not have glaucoma with a cup-to-disc ratio of greater than 0.8
3. The member does not have a torn or ruptured posterior lens capsule

Diabetic Macular Edema (DME)
Authorization of 12 months may be granted for treatment of diabetic macular edema when all of the following criteria are met:
1. The member does not have an ocular or periocular infection
2. The member does not have glaucoma with a cup-to-disc ratio of greater than 0.8
3. The member does not have a torn or ruptured posterior lens capsule

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Ozurdex.

B. The member is receiving benefit from therapy (e.g. stabilization of visual acuity or improvement in best corrected visual acuity (BCVA) score when compared to baseline)
C. The member has no evidence of unacceptable toxicity while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Ozurdex
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ozurdex are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Ozurdex [package insert]. Madison, NJ; Allergan USA, Inc.; December 2022. Accessed November 2023.

PADCEV (enfortumab vedotin-ejfv)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Padcev (enfortumab vedotin-ejfv), as a single agent, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy or are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.
2. Padcev, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who are not eligible for cisplatin-containing chemotherapy.

B. Compendial Indications
Urothelial carcinoma
1. Bladder cancer
2. Primary carcinoma of the urethra
3. Upper genitourinary (GU) tract tumors
4. Urothelial carcinoma of the prostate

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Urothelial Carcinoma

A. Authorization of 12 months may be granted for treatment of urothelial carcinoma as a single agent when used as subsequent therapy following platinum-containing chemotherapy and prior treatment with a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor or when used as subsequent therapy for members who are ineligible for cisplatin-containing chemotherapy for any of the following subtypes:
1. Urothelial carcinoma of the bladder in any of the following settings:
   a. Stage II disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with concurrent bladder preserving chemoradiotherapy and maximal transurethral resection of bladder tumor (TURBT)
   b. Locally advanced or metastatic disease
   c. Metastatic or local recurrence post-cystectomy
   d. Muscle invasive local recurrence or persistent disease in a preserved bladder
2. Primary carcinoma of the urethra with locally advanced, recurrent or metastatic disease.
3. Urothelial carcinoma of the upper genitourinary tract or urothelial carcinoma of the prostate with locally advanced or metastatic disease.

B. Authorization of 12 months may be granted for treatment of urothelial carcinoma in combination with pembrolizumab for members who are ineligible for cisplatin-containing chemotherapy for any of the following subtypes:
1. Urothelial carcinoma of the bladder in any of the following settings:

a. Stage II disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with concurrent bladder preserving chemoradiotherapy, and maximal transurethral resection of bladder tumor (TURBT)
b. Locally advanced or metastatic disease
c. Metastatic or local recurrence post-cystectomy
d. Muscle invasive local recurrence or persistent disease in a preserved bladder

2. Primary carcinoma of the urethra with locally advanced, recurrent or metastatic disease.
3. Urothelial carcinoma of the upper genitourinary tract or urothelial carcinoma of the prostate with locally advanced or metastatic disease

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
   1. No evidence of unacceptable toxicity while on the current regimen and
   2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Padcev.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Bladder cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Padcev are covered in addition to the following:

1. Bladder cancer
2. Primary carcinoma of the urethra
3. Upper genitourinary (GU) tract tumors
4. Urothelial carcinoma of the prostate

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Padcev to treat urothelial carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Padcev [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; April 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 2, 2023.

PEDMARK (sodium thiosulfate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
To reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors

Limitations of Use: The safety and efficacy of Pedmark have not been established when administered following cisplatin infusions longer than 6 hours. Pedmark may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted to reduce the risk of ototoxicity in pediatric members 1 month of age and older when both of the following criteria are met:
A. Member will be receiving cisplatin for treatment of localized, non-metastatic solid tumor
B. Cisplatin infusion will not be longer than 6 hours in duration

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all initial authorization criteria are met.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Pedmark.
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Pedmark are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Pedmark [package insert]. Hoboken, NJ: Fennec Pharmaceuticals, Inc.; September 2022

ALIMTA (pemetrexed)
PEMFEXY (pemetrexed)
PEMRYDI RTU (pemetrexed)
pemetrexed

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Non-squamous non-small cell lung cancer (NSCLC)
      a. In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EFGR or ALK genomic tumor aberrations.
      b. In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC).
      c. As a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
      d. As a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.

         Limitations of use: Pemetrexed is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer (NSCLC).

   2. Mesothelioma
      In combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

B. Compendial Uses
   1. Bladder cancer
   2. Pleural mesothelioma
   3. Peritoneal mesothelioma
   4. Pericardial mesothelioma
   5. Tunica vaginalis testis mesothelioma
   6. Nonsquamous non-small cell lung cancer (NSCLC)
   7. Ovarian cancer, fallopian tube cancer, and primary peritoneal cancer: epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, carcinosarcoma (malignant mixed Mullerian tumors), clear cell carcinoma of the ovary, grade 1 endometrioid carcinoma, low-grade serious carcinoma/ovarian borderline epithelial tumor (low malignant potential), and mucinous carcinoma of the ovary
   8. Primary central nervous system (CNS) lymphoma
   9. Thymomas and thymic carcinomas
   10. Cervical cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Bladder Cancer

Authorization of 6 months may be granted for treatment of locally advanced, metastatic, or relapsed transitional cell urothelium cancer, as second-line treatment.

B. Pleural or Peritoneal Mesothelioma
Authorization of 6 months may be granted for treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma, when any of the following criteria are met:
1. The requested medication will be used as a single agent or in combination with cisplatin or carboplatin; or
2. The requested medication will be used in combination with bevacizumab or durvalumab (Imfinzi), and either cisplatin or carboplatin.

C. Non-Small Cell Lung Cancer (Non-Squamous Histology)
Authorization of 6 months may be granted for treatment of non-squamous non-small cell lung cancer (including leptomeningeal metastases).

D. Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer
Authorization of 6 months may be granted for treatment of persistent or recurrent epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, carcinosarcoma (malignant mixed Mullerian tumors), clear cell carcinoma of the ovary, grade 1 endometrioid carcinoma, low-grade serious carcinoma/ovarian borderline epithelial tumor (low malignant potential), or mucinous carcinoma of the ovary, as single agent therapy.

E. Primary Central Nervous System (CNS) Lymphoma
Authorization of 6 months may be granted for treatment of primary CNS lymphoma, as a single agent.

F. Thymomas and Thymic Carcinomas
Authorization of 6 months may be granted for treatment of thymoma or thymic carcinoma, as a single agent.

G. Cervical Cancer
Authorization of 6 months may be granted for treatment of persistent, recurrent, or metastatic cervical cancer.

III. CONTINUATION OF THERAPY

A. All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for an indication in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Alimta, Pemfexy, Pemrydi RTU, and pemetrexed
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Any applicable guidelines
    a. NCCN Guideline: Central Nervous System Cancers
    b. NCCN Guideline: Mesothelioma (Pleural)
    c. NCCN Guideline: Mesothelioma (Peritoneal)
    d. NCCN Guideline: Bladder Cancer
    e. NCCN Guideline: Cervical Cancer
    f. NCCN Guideline: Non-Small Cell Lung Cancer

g. NCCN Guideline: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
h. NCCN Guideline: Thymomas and Thymic Carcinomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for pemetrexed are covered in addition to bladder cancer, mesothelioma, nonsquamous non-small cell lung cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, primary central nervous system (CNS) lymphoma, thymomas, thymic carcinomas, and cervical cancer.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Alimta, Pemfexy, Pemrydi RTU, and pemetrexed to treat bladder cancer, mesothelioma, nonsquamous non-small cell lung cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, primary central nervous system (CNS) lymphoma, thymomas, thymic carcinomas, and cervical cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

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2. Pemfexy [package insert]. Woodcliff Lake, NJ: Eagle Pharmaceuticals, Inc.; May 2023.
3. Pemetrexed disodium [package insert]. Princeton, NJ: Dr. Reddy's Laboratories Inc.; September 2022.
4. Pemrydi RTU [package insert]. Ahmedabad, India: Zydus Lifesciences Limited; June 2023.
5. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed November 2023.
6. Lexicomp [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed November 2023.
7. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com Accessed July 17, 2023.

PERJETA (pertuzumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Metastatic breast cancer
   In combination with trastuzumab and docetaxel for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

2. Neoadjuvant treatment of breast cancer
   In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

3. Adjuvant treatment of breast cancer
   In combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

B. Compendial Uses
1. HER2-positive breast cancer
2. HER2-amplified and RAS and BRAF wild-type colorectal cancer (including appendiceal adenocarcinoma and anal adenocarcinoma)
3. HER2-positive recurrent salivary gland tumors
4. HER2-positive biliary tract cancers

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: human epidermal growth factor receptor 2 (HER2) status, RAS mutation status (where applicable), BRAF mutation status (where applicable)

III. CRITERIA FOR INITIAL APPROVAL

A. Breast cancer
1. Authorization of 12 months may be granted for neoadjuvant treatment of HER2-positive breast cancer.
2. Authorization of 12 months may be granted for adjuvant treatment of HER2-positive breast cancer.
3. Authorization of 12 months may be granted for treatment of recurrent or metastatic HER2-positive breast cancer or HER2-positive breast cancer with no response to preoperative systemic therapy.

B. Colorectal Cancer
Authorization of 12 months may be granted for treatment of HER2-amplified and RAS and BRAF wild-type colorectal cancer (including appendiceal adenocarcinoma and anal adenocarcinoma) not previously treated with HER2 inhibitor.

C. Salivary Gland Tumors
Authorization of 12 months may be granted for treatment of HER2-positive salivary gland tumors.

D. Biliary Tract Cancer
Authorization of 12 months may be granted for subsequent treatment of unresectable or resected gross residual (R2) disease, or metastatic HER2-positive biliary tract cancers (including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for all members (including new members) when all of the following criteria are met:
A. The member is currently receiving treatment with requested medication
B. The requested medication is being used to treat a diagnosis or condition enumerated in Section III
C. For members requesting reauthorization for adjuvant or neoadjuvant treatment of breast cancer, the maximum treatment duration is 12 months.
D. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Perjeta.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN guideline: Breast cancer
4. NCCN guideline: Biliary tract cancers
5. NCCN guideline: Colon cancer
6. NCCN guideline: Head and neck cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Perjeta are covered in addition to the following:
1. HER2-positive breast cancer
2. HER2-amplified and RAS and BRAF wild-type colorectal cancer (including appendiceal adenocarcinoma and anal adenocarcinoma)
3. HER2-positive recurrent salivary gland tumors
4. HER2-positive biliary tract cancers

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Perjeta to treat the compendial indications in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Perjeta [package insert]. South San Francisco, CA: Genentech, Inc.; February 2021.

2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 29, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed November 29, 2023.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed November 29, 2023.

PHESGO (pertuzumab, trastuzumab, and hyaluronidase-zzxf)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Phesgo is indicated for use in combination with chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer

   2. Phesgo is indicated for use in combination with chemotherapy for the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.

   3. Phesgo is indicated for use in combination with docetaxel for the treatment of adult patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

B. Compendial Uses
   Treatment of recurrent human epidermal growth factor receptor 2 (HER2)-positive breast cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Human epidermal growth factor receptor 2 (HER2) status.

III. CRITERIA FOR INITIAL APPROVAL

Breast Cancer

A. Authorization of up to 12 months may be granted for pre-operative (neoadjuvant) treatment of HER2-positive breast cancer in combination with chemotherapy for locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive).
B. Authorization of up to 12 months may be granted for adjuvant treatment of HER2-positive breast cancer that is either node-positive or at high risk for recurrence in combination with chemotherapy.
C. Authorization of 12 months may be granted for the treatment of HER2-positive recurrent or metastatic breast cancer or HER2-positive breast cancer with no response to preoperative systemic therapy.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Adjuvant and neoadjuvant treatment of breast cancer
Authorization of 12 months (up to 12 months total) may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with requested medication
2. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

B. Breast Cancer with no response to preoperative therapy or in the recurrent, unresectable, advanced or metastatic setting

Authorization of 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with requested medication
2. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Phesgo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Breast cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Phesgo are covered in addition to recurrent HER2-positive breast cancer.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Phesgo to treat recurrent HER2-positive breast cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Phesgo [package insert]. South San Francisco, CA: Genentech, Inc; June 2020.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 4, 2023.
3. Von Minckwitz, G. *et al*. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N. Engl. J. Med.* 377, 122–131 (2017). Available at: https://www.nejm.org/doi/full/10.1056/nejmoa1703643

POLIVY (polatuzumab vedotin-piiq)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
1. Polivy in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.
2. Polivy in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high-grade B-cell lymphoma (HGBL) and who have an International Prognostic Index score of 2 or greater.

B. Compendial Uses
B-cell Lymphomas
1. High-grade B-cell lymphomas (HGBLs)
2. Monomorphic post-transplant lymphoproliferative disorders (B-cell type)
3. Human Immunodeficiency Virus (HIV) Related B-cell lymphomas (HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, HIV-related plasmablastic lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma)
4. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
5. Follicular lymphoma
6. Diffuse large B-cell Lymphoma (DLBCL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Diffuse large B-cell lymphoma (DLBCL)
Authorization of 6 months (up to 6 cycles) may be granted for treatment of DLBCL in any of the following settings:
1. The requested drug is used as subsequent treatment as a single agent, or in combination with bendamustine with or without rituximab for relapsed or refractory disease when the member is not a candidate for transplant, or the requested medication will be used as a bridging option until CAR T-cell product is available.
2. The requested drug will be used as first line therapy for stage II-IV disease in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) in members who have an International Prognostic Index score of 2 or greater (low intermediate-high).

B. High-grade B-cell lymphomas (HGBLs)
Authorization of 6 months (for up to 6 cycles) may be granted for treatment of high-grade B-cell lymphomas (HGBLs) (also referred to as “double-hit” or “triple-hit” lymphomas) when anyof the following criteria are met:
1. The requested drug is used as subsequent treatment as a single agent, or in combination with bendamustine with or without rituximab and member is not a candidate for transplant or the requested medication will be used as a bridging option until CAR T-cell product is available.

2. The requested drug will be used as first line therapy in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) and member has an International Prognostic Index score of 2 or greater.

C. Monomorphic post-transplant lymphoproliferative disorders (B-cell type)
Authorization of 6 months (for up to 6 cycles) may be granted for subsequent treatment of post-transplant lymphoproliferative disorders when all the following criteria are met:
1. The requested drug is used as a single agent, or in combination with bendamustine with or without rituximab
2. Member is not a candidate for transplant or the requested medication will be used as a bridging option until CAR T-cell product is available.

D. Human Immunodeficiency Virus (HIV) Related B-cell lymphomas (HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, HIV-related plasmablastic lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma)
Authorization of 6 months (for up to 6 cycles) may be granted for subsequent treatment of HIV-related B-cell lymphomas when all of the following criteria are met:
1. The requested drug is used as a single agent, or in combination with bendamustine with or without rituximab
2. Member is not a candidate for transplant or the requested medication will be used as a bridging option until CAR T-cell product is available.

E. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma (DLBCL)
Authorization of 6 months (for up to 6 cycles) may be granted for subsequent treatment of histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma when all of the following criteria are met:
1. The requested drug is used as a single agent, or in combination with bendamustine with or without rituximab
2. Member is not a candidate for transplant.

F. Follicular lymphoma
Authorization of 6 months (for up to 6 cycles) may be granted for subsequent treatment of follicular lymphoma when the requested drug is used as a single agent, or in combination with bendamustine with or without rituximab

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization up to 6 months (6 cycles total) may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested drug.
B. The requested drug is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen AND
   ii. No evidence of disease progression while on the current regimen.
D. The member has received less than 6 cycles of the requested drug.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Polivy.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs

e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Polivy are covered in addition to the following:

1. High-grade B-cell lymphomas (HGBLs)
2. Monomorphic post-transplant lymphoproliferative disorders (B-cell type)
3. Human Immunodeficiency Virus (HIV) Related B-cell lymphomas (HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, HIV-related plasmablastic lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma)
4. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
5. Follicular lymphoma
6. Diffuse large B-cell Lymphoma (DLBCL)

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Polivy to treat the compendial indications listed in section IV can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Polivy [package insert]. South San Francisco, CA: Genentech, Inc.; April 2023.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 2.2023. https://www.nccn.org. Accessed April 4, 2023.
3. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 4, 2023.
4. Micromedex Solutions [database online]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/. Accessed April 4, 2023.
5. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;386:351-363. DOI: 10.1026/NEJMoa2115304.
6. Clinical Consult: CVS Caremark Clinical Programs Review. Focus on Hematology – Oncology Clinical Programs. July 2022.

POMBILITI (cipaglucosidase alfa-atga)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Pombiliti is indicated, in combination with Opfolda, for the treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing greater than or equal to 40 kg and who are not improving on their current enzyme replacement therapy (ERT).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: acid alpha-glucosidase enzyme assay or genetic testing results supporting diagnosis.
B. Continuation or therapy: chart notes documenting a positive response to therapy.

III. CRITERIA FOR INITIAL APPROVAL

Late-onset Pompe disease
Authorization of 12 months may be granted for treatment of late-onset Pompe disease when all of the following criteria are met:
A. Member is 18 years of age or older.
B. Member weighs greater than or equal to 40 kg.
C. Diagnosis was confirmed by enzyme assay demonstrating a deficiency of acid alpha-glucosidase enzyme activity or by genetic testing.
D. Member is not improving on current enzyme replacement therapy (ERT) (e.g., Lumizyme, Nexviazyme).
E. The requested medication will be taken in combination with Opfolda (miglustat).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, walking capacity, respiratory function, or muscle strength).
D. The requested medication will be taken in combination with Opfolda (miglustat).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Pombiliti.
2. The available compendium

a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. Pompe Disease, Gene Reviews article.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Pombiliti are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assay and genetic testing to diagnose Pompe disease can be found in a Gene Reviews article. The diagnosis of Pompe disease is established in a patient with either deficiency of acid alpha-glucosidase enzyme activity or biallelic pathogenic variants in GAA on molecular genetic testing.

VII. REFERENCES

1. Pombiliti [package insert]. Philadelphia, PA: Amicus Therapeutics US, LLC; September 2023.
2. Leslie N, Bailey L. Pompe Disease. 2007 Aug 31 [Updated Nov 2, 2023]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2023.

PORTRAZZA (necitumumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Portrazza is indicated for the first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) in combination with gemcitabine and cisplatin.

Limitation of Use: Portrazza is not indicated for the treatment of non-squamous non-small cell lung cancer.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Non-small cell lung cancer (NSCLC)
Authorization of 12 months may be granted for treatment of metastatic squamous NSCLC when the requested medication is used in combination with gemcitabine and cisplatin.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Portrazza.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Portrazza are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Portrazza [package insert]. Indianapolis, IN: Eli Lilly and Company; November 2015.

POTELIGEO (mogamulizumab-kpkc)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Poteligeo is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

B. Compendial Uses
1. Mycosis fungoides (MF) or Sézary syndrome (SS) as primary treatment
2. Adult T-cell leukemia/lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Mycosis fungoides (MF) or Sézary syndrome (SS)
Authorization of 12 months may be granted for treatment of mycosis fungoides (MF) or Sézary syndrome (SS).

B. Adult T-cell leukemia/lymphoma
Authorization of 12 months may be granted for treatment of adult T-cell leukemia/lymphoma as a single agent when used as subsequent therapy for chronic high risk, acute, or lymphoma subtypes.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Poteligeo
B. Poteligeo is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
1. No evidence of unacceptable toxicity while on the current regimen AND
2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Poteligeo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Primary cutaneous lymphomas

4. NCCN Guideline: T-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Poteligeo are covered in addition to the following:

1. Mycosis fungoides (MF) or Sézary syndrome (SS) as primary treatment
2. Adult T-cell leukemia/lymphoma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Poteligeo to treat mycosis fungoides/Sezary syndrome and adult T-cell leukemia/lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Poteligeo [package insert]. Bedminster, NJ: Kyowa Kirin, Inc.; March 2022.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed January 4, 2024.

PROLEUKIN (aldesleukin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Proleukin is indicated for the treatment of adults with metastatic renal cell carcinoma (metastatic RCC).
   2. Proleukin is indicated for the treatment of adults with metastatic melanoma.

B. Compendial Uses
   1. Relapsed or stage IV renal cell carcinoma
   2. Unresectable cutaneous melanoma
   3. Chronic graft-versus-host disease (GVHD)
   4. Acute Myeloid Leukemia (AML)
   5. Carcinomatous metastasis in skin
   6. Glial tumor of the brain
   7. Kaposi's Sarcoma
   8. Malignant Effusion

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Renal Cell Carcinoma
Authorization of 6 months may be granted for treatment of relapsed or stage IV renal cell carcinoma with clear cell histology for high-dose single-agent therapy.

B. Cutaneous Melanoma
Authorization of 6 months may be granted for treatment of cutaneous melanoma when used as one of the following:
   1. Intravenously as high-dose single agent subsequent therapy for metastatic or unresectable disease.
   2. Intralesionally for unresectable disease

C. Chronic graft-versus-host disease (GVHD)
Authorization of 6 months may be granted for treatment of chronic graft-versus host-disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response to first-line therapy options.

D. Acute Myeloid Leukemia (AML)
Authorization of 6 months may be granted for the treatment of AML when used as high-dose therapy.

E. Carcinomatous metastasis in skin
Authorization of 6 months may be granted for treatment of skin metastasis (carcinoma erysipeloids) from gastric carcinoma when used intralesionally.

F. Glial tumor of brain

Authorization of 6 months may be granted for treatment of refractory anaplastic astrocytoma when used intracerebrally in combination with lymphokine-activated killer cells.

G. Kaposi's Sarcoma
Authorization of 6 months may be granted for the treatment of classic Kaposi's Sarcoma not associated with human immunodeficiency virus when used intralesionally.

H. Malignant Effusion
Authorization of 6 months may be granted when given at a low dose for treatment of neoplastic fluid accumulation in members with advanced solid tumors.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Renal Cell Carcinoma or Cutaneous Melanoma
Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member must be evaluated for response approximately 4 weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next treatment course.
3. Additional courses of treatment should be given only if there is some tumor shrinkage following the last course.
4. Retreatment is not contraindicated.
5. Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge.

B. Chronic graft-versus-host disease (GVHD)
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy. Benefit is defined as:
   a. Improvement in symptoms, and
   b. No unacceptable toxicity

C. All other indications
Authorization for 12 months may be granted for all members who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat any other diagnosis or condition enumerated in Section II.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen AND
   b. No evidence of disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Proleukin.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Cutaneous melanoma
4. NCCN Guideline: Hematopoietic cell transplantation
5. NCCN Guideline: Kidney cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Proleukin are covered in addition to the following:

1. Relapsed or stage IV renal cell carcinoma
2. Unresectable cutaneous melanoma
3. Chronic graft-versus-host disease (GVHD)
4. Acute Myeloid Leukemia (AML)
5. Carcinomatous metastasis in skin
6. Glial tumor of the brain
7. Kaposi's Sarcoma
8. Malignant Effusion

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Proleukin to treat renal cell carcinoma and cutaneous melanoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Proleukin to treat acute myeloid leukemia, carcinomatous metastasis in skin, glial tumor of brain, and Kaposi's sarcoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Proleukin to treat chronic graft-versus-host disease can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of Proleukin in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using Proleukin to treat malignant effusion can be found in a study by Lissoni and colleagues. In a case-series study of patients with advanced solid tumors and neoplastic effusions (n=100), the intracavity administration of low-dose interleukin-2 (6,000,000 IU on days 1 and 7) resulted in an objective clinical response in 72% of patients with a median response duration of 5 months. A complete response was observed in 27% and a partial response in 45% of patients. The peritoneal site was significantly less responsive than the pleural or pericardial sites. The intracavity injection was well-tolerated.

VI. REFERENCES

1. Proleukin [package insert]. Yardley, PA: Clinigen, Inc.; September 2019.
2. The NCCN Drugs & Biologic Compendium 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed May 11, 2023.
3. Micromedex (electronic version). Truven Health Analytics. Greenwood Village, Colorado, USA http://www.micromedexsolutions.com/. Accessed May 11, 2023.
4. Lissoni P, Mandala M, Curigliano G, et al: Progress report on the palliative therapy of 100 patients with neoplastic effusions by intracavitary low-dose interleukin-2. Oncology 2001; 60:308-312.

PROLIA (denosumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA approved Indications
1. Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
2. Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
3. Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture, who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.
4. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.
5. Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

B. Compendial Uses
1. Prevention of osteoporosis in osteopenic postmenopausal women
2. Prevention or treatment of osteoporosis during androgen deprivation therapy for prostate cancer in patients with high fracture risk
3. Consider in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Osteoporosis treatment
Authorization of 12 months may be granted for treatment of osteoporosis in men or postmenopausal women at high risk for fracture.

B. Osteoporosis prevention
Authorization of 12 months may be granted for prevention of osteoporosis in osteopenic postmenopausal women.

C. Increasing bone mass in prostate cancer
Authorization of 12 months may be granted to increase bone mass in men at high risk for fracture who are receiving androgen deprivation therapy for prostate cancer.

D. Increasing bone mass in breast cancer
Authorization of 12 months may be granted to increase bone mass in women at high risk for fracture who are receiving adjuvant aromatase inhibition therapy for breast cancer.

E. Glucocorticoid-induced osteoporosis

Authorization of 12 months may be granted to increase bone mass in men and women with glucocorticoid-induced osteoporosis at high risk for fracture.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Prolia
B. Prolia is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Prolia.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Prostate cancer
4. NCCN Guideline: Breast cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Prolia are covered in addition to the following:
A. Prevention of osteoporosis in osteopenic postmenopausal women
B. Prevention or treatment of osteoporosis during androgen deprivation therapy for prostate cancer in patients with high fracture risk
C. Maintenance or improvement in bone mineral density in postmenopausal patients receiving adjuvant aromatase inhibition therapy

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Prolia for prevention of osteoporosis in osteopenic postmenopausal women as an approvable indication is evidenced by a multicenter, randomized, placebo-controlled study of 332 postmenopausal women with low bone mineral density (BMD) by Bone et al. Treatment with denosumab given once every 6 months improved BMD from baseline compared with placebo at 2 years. Postmenopausal women (mean age, 59.4 +/- 7.5 years) were eligible for enrollment if they had a lumbar spine (LS)-BMD T-score of -1 to -2.5 (mean T-score, -1.61 +/- 0.42), no history of fracture after age 25 years, and had not received IV bisphosphonates, fluoride, or strontium within the previous 5 years or parathyroid hormone agents (including derivatives), steroids, hormone-replacement therapy, selective estrogen-receptor modulators, calcitonin, or calcitriol within the previous 6 weeks. Patients were randomized to receive either denosumab 60 mg (n=166) or placebo (n=166) given subcutaneously every 6 months. All patients also received oral calcium (1000 mg) and vitamin D (400 to 800 international units or greater) daily. Approximately 86% of patients completed 24 months of study treatment. At 24 months, patients in the denosumab arm had a mean percentage LS-BMD increase over baseline (6.5%; 97.5% CI, 5.8% to 7.2%) and patients in the placebo arm had a mean percentage LS-BMD decrease over baseline (-0.6%; 97.5% CI, -1.2% to 0.1%); additionally, the mean percentage LS-BMD difference between the 2 arms was significant (7%; 97.5% CI, 6.2% to 7.8%; p less than 0.0001). In patients who received denosumab, mean percentage BMDs were all increased from baseline at 24 months for the total hip (3.4%; 97.5% CI, 3% to 3.7%), femoral neck (2.8%; 97.5% CI, 2.3% to 3.3%), trochanter (5.2%; 97.5% CI, 4.7% to 5.6%), and distal third of the radius (1.4%; 97.5% CI, 0.9% to 1.9%), and

the mean percent BMD differences compared with placebo were significant (p less than 0.0001). Markers of bone turnover were reduced from baseline in patients receiving denosumab (mean percent reduction: C-telopeptide I, 63% to 88%; tartrate-resistant acid phosphatase 5b, 40% to 50%; intact N-terminal propeptide of type 1 procollagen, 65% to 76%).

Support for using Prolia for the prevention or treatment of osteoporosis during androgen deprivation therapy is found in the National Comprehensive Cancer Network's guideline for prostate cancer. The NCCN Guideline for prostate cancer supports the use of Prolia as prevention or treatment of osteoporosis during androgen deprivation therapy in patients with high fracture risk.

Support for using Prolia to maintain or improve bone mineral density and reduce the risk of fractures in postmenopausal patients receiving adjuvant aromatase inhibition therapy is found in the National Comprehensive Cancer Network's guideline for breast cancer. The NCCN Guideline for breast cancer supports the use of Prolia in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce the risk of fractures.

VI. REFERENCES

1. Prolia [package insert]. Thousand Oaks, CA: Amgen Inc.; January 2023.
2. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado. Available at https://www.micromedexsolutions.com Accessed October 3, 2023.
3. The NCCN Drugs & Biologics Compendium© 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed October 5, 2023.
4. Bone HG, Bolognese MA, Yuen CK, et al: Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab.* 2008; 93(6):2149-2157.

PROVENGE (sipuleucel-T)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Provenge (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer.

B. Compendial Use
Biochemical relapse of nonmetastatic androgen-dependent (castration-naïve) prostate cancer

C. CMS Nationally Covered Use
The following NCD policy applies to these criteria: Autologous Cellular Immunotherapy Treatment (110.22).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Prostate cancer
Authorization of 6 months may be granted when the requested medication is prescribed for a maximum of 3 doses for either of the following indications:
A. Asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer
B. Biochemical relapse of nonmetastatic androgen-dependent (castration-naïve) prostate cancer

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

The requested medication is administered every 2 weeks for a total of 3 doses. Authorization for 3 months to complete the 3-dose treatment may be granted when all of the following criteria are met:
A. The member is currently receiving treatment with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member has not yet completed treatment with all 3 doses

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Provenge.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs

e. Clinical Pharmacology
3. NCCN Guideline: Prostate cancer
4. NCD 110.22- Autologous Cellular Immunotherapy Treatment

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Provenge are covered in addition to biochemically-relapsed, androgen-dependent prostate cancer.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Provenge to treat biochemically-relapsed, androgen-dependent prostate cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer is covered according to the conditions outlined in National Coverage Determination Manual section 110.22- Autologous Cellular Immunotherapy Treatment.

VI. REFERENCES

1. Provenge [package insert]. Seal Beach, CA: Dendreon Pharmaceuticals LLC; July 2017.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 7, 2023.
3. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed August 7, 2023.
4. National Coverage Determination (NCD) for Autologous Cellular Immunotherapy Treatment (110.22). Version 1. http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=344&ncdver=1&DocID=110.22&from2=search.asp&bc=gAAAAAgAAAAA& Accessed August 7, 2023.

QALSODY (tofersen)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Qalsody is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.

This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain observed in patients treated with Qalsody. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available upon request for all submissions: Supporting chart notes or medical record as applicable to Section IV and V.

A. Initial Requests:
   1. Member has weakness attributable to ALS confirmed by diagnostic testing (e.g., imaging, nerve conduction studies, laboratory results to support the diagnosis).
   2. Genetic testing confirming SOD1 mutation.
B. Continuation Requests:
   1. Documentation of clinical benefit from Qalsody therapy.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a neurologist, neuromuscular specialist, or physician specializing in the treatment of amyotrophic lateral sclerosis (ALS).

IV. CRITERIA FOR INITIAL APPROVAL

Amyotrophic Lateral Sclerosis (ALS)
Authorization of 12 months may be granted for treatment of ALS when both of the following criteria are met:

A. Member is 18 years of age or older.
B. Member has weakness attributable to ALS confirmed by diagnostic testing (e.g., medical history and/or diagnostic testing including nerve conduction studies, imaging and laboratory values to support the diagnosis).
C. Genetic testing confirming a SOD1 mutation.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving treatment with Qalsody.
B. Qalsody is being used for the treatment of weakness associated with ALS in members who have a mutation in the SOD1 gene.
C. There is a clinical benefit from Qalsody therapy.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Qalsody.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Qalsody are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCES

1. Qalsody [package insert]. Cambridge, MA: Biogen MA, Inc.; April 2023.

RADICAVA (edaravone)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. REQUIRED DOCUMENTATION

The following documentation must be available upon request for all submissions:
A. For initial approval, chart notes confirming diagnosis of definite or probable ALS (e.g., medical history and diagnostic testing including, nerve conduction studies, imaging and laboratory values to support the diagnosis)
B. For initial approval, chart notes or documentation confirming the member has scores of at least 2 points on all 12 areas of the revised ALS Functional Rating Scale (ALSFRS-R)
C. For continuation of therapy, documentation of clinical benefit from Radicava therapy

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a neurologist, neuromuscular specialist, or physician specializing in the treatment of amyotrophic lateral sclerosis (ALS).

IV. CRITERIA FOR INITIAL APPROVAL

Amyotrophic Lateral Sclerosis (ALS)
Authorization of 12 months may be granted for treatment of ALS when both of the following criteria are met:
A. Diagnosis of definite or probable ALS (e.g., medical history and diagnostic testing including, nerve conduction studies, imaging and laboratory values to support the diagnosis)
B. Member has scores of at least 2 points on all 12 areas of the revised ALS Functional Rating Scale (ALSFRS-R)

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving treatment with Radicava.
B. Radicava is being used for the treatment of definite or probable ALS.
C. There is a clinical benefit from Radicava therapy.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Radicava.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Radicava are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCES

1. Radicava [package insert]. Jersey City, NJ: MT Pharma America, Inc.; May 2022.
2. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis; Andersen PM, et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. *Eur J Neurol*. 2012;19(3):360-75.

REBLOZYL (luspatercept-aamt)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. Treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions
B. Treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions
C. Treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

Limitations of Use: Reblozyl is not indicated for use as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

A. Anemia with beta thalassemia
The following documentation must be available, upon request, for all submissions for initial therapy requests:
1. Pretreatment or pretransfusion hemoglobin (Hgb) level.
2. Either of the following:
   i. Hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) results OR molecular genetic testing results, or
   ii. Chart notes or medical record documentation stating diagnosis of beta thalassemia (β-thalassemia) or hemoglobin E/β-thalassemia was previously confirmed

B. Anemia of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm
The following documentation must be available, upon request, for all submissions for initial therapy requests: Pretreatment or pretransfusion hemoglobin (Hgb) level

III. EXCLUSIONS

Coverage will not be provided for treatment of anemia with beta thalassemia in members with hemoglobin S/β-thalassemia or alpha-thalassemia.

IV. CRITERIA FOR INITIAL APPROVAL

A. Anemia with beta thalassemia
Authorization of 16 weeks may be granted for treatment of anemia with beta thalassemia in members 18 years of age or older when all of the following criteria are met:

1. The member has symptomatic anemia evidenced by a pretreatment or pretransfusion Hgb level less than or equal to 11 g/dL (grams per deciliter).
2. The member has a diagnosis of beta thalassemia (β-thalassemia) or hemoglobin E/β-thalassemia (β-thalassemia with mutation and/or multiplication of alpha globin is allowed) confirmed by one of the following:
    i. Hemoglobin electrophoresis or high-performance liquid chromatography (HPLC)
    ii. Molecular genetic testing
3. The member required at least 6 red blood cell (RBC) units to be transfused in the previous 24 weeks.

Note: If a red blood cell (RBC) transfusion occurred prior to dosing, the pretransfusion hemoglobin (Hgb) level must be considered for dosing purposes.

B. Anemia of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm
Authorization of 24 weeks may be granted for treatment of anemia of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm in patients 18 years of age or older when all of the following criteria are met:
1. The member has one of the following:
    i. Very low- to intermediate-risk myelodysplastic syndrome
    ii. Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
2. The member has symptomatic anemia evidenced by a pretreatment or pretransfusion Hgb level less than or equal to 11 g/dL.
3. The member has been receiving regular red blood cell (RBC) transfusions as defined by greater than or equal to 2 units per 8 weeks.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Reblozyl
B. Reblozyl is being used to treat an indication enumerated in Section IV
C. The member is receiving benefit from therapy. Benefit is defined as meeting all of the following criteria:
    1. Achieving or maintaining red blood cell transfusion burden reduction
    2. No evidence of unacceptable toxicity from Reblozyl.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Reblozyl.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. A phase 3 trial of luspatercept in patients with transfusion-dependent β-thalassemia
4. Luspatercept in patients with lower-risk myelodysplastic syndromes
5. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia
6. NCCN Guideline: Myelodysplastic syndromes

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Reblozyl are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using either hemoglobin electrophoresis, high-performance liquid chromatography (HPLC) or molecular genetic testing is supported by the 2021 Thalassemia International Federation guidelines for the management of transfusion-dependent thalassemia. The diagnosis of thalassemias relies on using red blood cell indices, hemoglobin analysis, and assessing the clinical severity of anemia. Molecular genetic testing may be useful for predicting the clinical phenotype and enabling presymptomatic diagnosis of at-risk family members and prenatal diagnosis.
According to the UpToDate database, the diagnostic evaluation of a thalassemia depends on the personal and family history and available laboratory results. Genetic testing is used for precise diagnosis and is especially important in carrier detection, prenatal testing, and genetic counseling. Genetic testing can be done by gene sequencing or a number of other methods. If genetic testing is not available, hemoglobin can be analyzed using a number of protein chemistry methods. The most commonly used methods are HPLC and various hemoglobin electrophoresis techniques.

VIII. REFERENCES

1. Reblozyl [package insert]. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; August 2023.
2. Capellini MD, Viprakasit V, Taher AT, et al. A phase 3 trial of luspatercept in patients with transfusion-dependent β-thalassemia. *N Engl J Med*. 2020;382:1219-31.
3. Benz EJ, Angelucci E. Diagnosis of thalassemia (adults and children). In: UpToDate, Timauer, JS (Ed), UpToDate, Waltham, MA, 2023. URL: www.uptodate.com. Accessed October 3, 2023.
4. National Comprehensive Cancer Network. The NCCN Drugs & Biologics Compendium. http://www.nccn.org. Accessed September 5, 2023.
5. Fenaux P, Platzbecker U, Mufti GJ, et.al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382:140-51.
6. Farmakis D, Porter J, Taher A, Cappellini MD, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. *Hemasphere*. 2022;6(8):e732.

RETHYMIC (allogenic processed thymus tissue-agdc)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Rethymic is indicated for immune reconstitution in pediatric patients with congenital athymia.

Limitations of use: Rethymic is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

A. The following documentation must be available, upon request, for all submissions:
   1. Medical record documentation (i.e., chart notes) confirming the diagnosis.

III. CRITERIA FOR INITIAL APPROVAL

A. Congenital Athymia
The requested drug will be covered with prior authorization when all of the following criteria are met:
   1. The patient has congenital athymia
   2. The request is for immune reconstitution in a pediatric patient
   3. The request is not for treatment of severe combined immunodeficiency (SCID)
   4. The patient has not previously received Rethymic

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Rethymic
2. The available compendium
   a. Micromedex DrugDex
   b. American Hospital Formulary Service- Drug Information (AHFS-DI)
   c. Lexi-Drugs
   d. Clinical Pharmacology
3. Any applicable guidelines (Examples listed below)
   a. Clinical practice guidelines for the immunological management of chromosome 22q11.2 deletion syndrome and other defects in thymic development

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rethymic are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Rethymic [package insert]. Cambridge, MA; Enzyvant Therapeutics, Inc.; 2023. Accessed August 2023.

2. Mustillo PJ, Sullivan KE, Chinn IK, et al. Clinical practice guidelines for the immunological management of chromosome 22q11.2 deletion syndrome and other defects in thymic development. *J Clin Immunol*. 2023;43(2):247-270. doi:10.1007/s10875-022-01418-y

RETISERT (fluocinolone acetonide intravitreal implant)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Retisert is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Non-infectious Uveitis (NIU)
Authorization of 12 months may be granted for treatment of chronic non-infectious uveitis when all of the following criteria are met:
1. The member has a diagnosis of chronic non-infectious uveitis affecting the posterior segment of the eye
2. The member does not have an active ocular or periocular viral, bacterial, mycobacterial, or fungal infection

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Retisert.
B. The member is receiving benefit from therapy (e.g. stabilization of visual acuity or improvement in BCVA score when compared to baseline, improvement in vitreous haze score)
C. The member has no evidence of unacceptable toxicity while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Retisert
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Retisert are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Retisert [package insert]. Bridgewater, NJ; Bausch & Lomb, Inc., division of a Bausch Health US, LLC; January 2021. Accessed November 2023.

REVCOVI (elapegademase-lvlr)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Revcovi is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Adenosine Deaminase Severe Combined Immune Deficiency (ADA-SCID)
Authorization of 12 months may be granted to members for treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) due to adenosine deaminase (ADA) deficiency.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Revcovi.
B. The member is receiving benefit from therapy (e.g. disease stability and/or improvement)
C. The member has no evidence of unacceptable toxicity while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Revcovi
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Revcovi are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Revcovi [package insert]. Cary, NC; Chiesi USA, Inc.; August 2022. Accessed November 2023.

RITUXAN HYCELA (rituximab and hyaluronidase human)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Adult patients with follicular lymphoma (FL):
      a. Relapsed or refractory, follicular lymphoma as a single agent
      b. Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
      c. Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy
   2. Adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens
   3. Adult patients with previously untreated and previously treated chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide (FC)

   Limitations of Use:
   Initiate treatment with Rituxan Hycela only after patients have received at least one full dose of a rituximab product by intravenous infusion.
   Rituxan Hycela is not indicated for the treatment of non-malignant conditions

B. Compendial Uses
   1. B-cell lymphomas:
      a. Castleman's disease (CD)
      b. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
      c. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
      d. Marginal zone lymphomas
         i. Nodal marginal zone lymphoma
         ii. Extranodal Marginal Zone Lymphoma (Gastric and Nongastric mucosa associated lymphoid tissue {MALT} lymphoma)
         iii. Splenic marginal zone lymphoma
      e. Mantle cell lymphoma
   2. Post-transplant lymphoproliferative disorder (PTLD)
   3. Hairy cell leukemia
   4. Primary cutaneous B-cell lymphoma (e.g., cutaneous marginal zone lymphoma or cutaneous follicle center lymphomas)
   5. Small lymphocytic lymphoma (SLL)
   6. Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma
   7. Hodgkin lymphoma, nodular lymphocyte-predominant

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Prior to initiating therapy, all members must receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions.

A. Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
Authorization of 12 months may be granted for treatment of CD20 positive CLL or SLL.

B. Hairy cell leukemia (HCL)
Authorization of 12 months may be granted for treatment of CD20 positive HCL.

C. B-cell lymphomas
Authorization of 12 months may be granted for treatment of any of the following oncologic disorders that are CD20-positive as confirmed by testing or analysis:

1. Castleman's disease (CD)
2. Diffuse large B-cell lymphoma (DLBCL)
3. Follicular lymphoma
4. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
5. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
6. Mantle cell lymphoma
7. Nodal marginal zone lymphoma
8. Post-transplant lymphoproliferative disorder (PTLD)
9. Marginal zone lymphomas
    i. Nodal marginal zone lymphoma
    ii. Extranodal Marginal Zone Lymphoma (Gastric and Nongastric MALT lymphoma)
    iii. Splenic marginal zone lymphoma

D. Primary cutaneous B-cell lymphoma
Authorization of 12 months may be granted for treatment of CD20 positive primary cutaneous B-cell lymphoma (e.g., cutaneous marginal zone lymphoma or cutaneous follicle center lymphomas).

E. Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma
Authorization of 12 months may be granted for treatment of CD20 positive Waldenström macroglobulinemia/ lymphoplasmacytic lymphoma.

F. Hodgkin lymphoma, nodular lymphocyte-predominant
Authorization of 12 months may be granted for treatment of CD20 positive Hodgkin lymphoma, nodular lymphocyte-predominant.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat an indication enumerated in Section II.
3. The member is receiving benefit from therapy. Benefit is defined as no unacceptable toxicity while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Rituxan Hycela.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex

c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Hairy cell leukemia
4. NCCN Guideline: Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
5. NCCN Guideline: Hodgkin lymphoma
6. NCCN Guideline: Primary cutaneous lymphomas
7. NCCN Guideline: Chronic lymphocytic leukemia/small lymphocytic lymphoma
8. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rituxan Hycela are covered in addition to the following:

1. B-cell lymphomas:
   a. Castleman's disease (CD)
   b. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
   c. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
   d. Marginal zone lymphomas
      i. Nodal marginal zone lymphoma
      ii. Extranodal Marginal Zone Lymphoma (Gastric and Nongastric mucosa associated lymphoid tissue {MALT} lymphoma)
      iii. Splenic marginal zone lymphoma
   e. Mantle cell lymphoma
2. Post-transplant lymphoproliferative disorder (PTLD)
3. Hairy cell leukemia
4. Primary cutaneous B-cell lymphoma (e.g., cutaneous marginal zone lymphoma or cutaneous follicle center lymphomas)
5. Small lymphocytic lymphoma (SLL)
6. Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma
7. Hodgkin lymphoma, nodular lymphocyte-predominant

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Rituxan Hycela for the compendial uses listed in section IV can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Rituxan Hycela [package insert]. South San Francisco, CA: Genentech, Inc.; June 2021.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 4, 2023.

RITUXAN (rituximab)
RUXIENCE (rituximab-pvvr)
TRUXIMA (rituximab-abbs)
RIABNI (rituximab-arrx)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Rituxan is indicated for the treatment of pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy.

Rituxan, Ruxience, Truxima, and Riabni are indicated for:
1. Non-Hodgkin's Lymphoma (NHL) in adult patients with:
   i. Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
   ii. Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
   iii. Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy
   iv. Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens
2. Chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.
3. Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis, in combination with glucocorticoids.
4. Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies.

Rituxan is also indicated for:
Pemphigus Vulgaris (PV):
Rituxan is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris.

B. Compendial Uses
1. B-cell lymphoma
   i. Human Immunodeficiency Virus (HIV) related B-cell lymphoma
   ii. Burkitt lymphoma
   iii. Castleman's disease
   iv. Diffuse large B-cell lymphoma
   v. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
   vi. Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma[3]
   vii. Follicular lymphoma
   viii. Mantle cell lymphoma
   ix. Marginal zone lymphoma (nodal, extranodal {gastric and non-gastric mucosa associated lymphoid tissue (MALT) lymphoma}, splenic)
   x. Post-transplant lymphoproliferative disorder (PTLD)
   xi. Pediatric aggressive mature B-cell lymphomas[3]

xii. B-cell lymphoblastic lymphoma
xiii. Primary Mediastinal Large B-Cell Lymphoma
2. Malignant ascites, in advanced low-grade non-Hodgkin lymphoma
3. B-cell acute lymphoblastic leukemia (ALL)
4. CLL/small lymphocytic lymphoma (SLL)
5. Hairy cell leukemia
6. Rosai-Dorfman disease
7. Hodgkin's lymphoma, nodular lymphocyte-predominant
8. Hodgkin's lymphoma, CD20-positive, relapsed or progressive
9. Primary cutaneous B-cell lymphoma
10. Central nervous system (CNS) cancers
    i. Leptomeningeal metastases from lymphomas
    ii. Primary CNS lymphoma
11. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
12. Rheumatoid arthritis, moderate or high disease activity despite disease-modifying anti-rheumatic drug (DMARD) monotherapy
13. Autoimmune hemolytic anemia
14. Immune or idiopathic thrombocytopenic purpura (ITP), as initial therapy
15. Immune or idiopathic thrombocytopenic purpura (ITP), relapsed/refractory to standard therapy (e.g., corticosteroids, immune globulin)
16. Thrombotic thrombocytopenic purpura
17. Relapsing-remitting multiple sclerosis
18. Primary progressive multiple sclerosis
19. Myasthenia gravis, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
20. Systemic lupus erythematosus, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
21. Sjögren's syndrome
22. Chronic graft-versus-host disease (GVHD)
23. Prevention of Epstein-Barr virus (EBV)-related PTLD in hematopoietic stem cell transplant in (HSCT) recipients
24. Evans syndrome
25. Nephrotic syndrome, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
26. Acquired factor VIII deficiency (acquired hemophilia A)
27. Idiopathic inflammatory myopathy, refractory
28. Immune checkpoint inhibitor-related toxicities
29. Allogeneic transplant conditioning
30. Lung disease with systemic sclerosis
31. Thyroid eye disease (moderate to severe)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Rheumatoid arthritis

Authorization of 12 months may be granted for treatment of rheumatoid arthritis when any of the following criteria are met.

1. The member has previously received treatment with a biologic or targeted synthetic DMARD (e.g., TNF inhibitor, JAK inhibitor) for the treatment of rheumatoid arthritis.
2. The member has had an inadequate response to methotrexate or leflunomide or there is a clinical reason to avoid treatment with methotrexate or leflunomide (e.g., renal or hepatic impairment).

B. Oncologic indications

Oncologic disorders must be CD20-positive as confirmed by testing or analysis to identify the CD20 protein on the surface of the B-cell.

1. B-cell lymphoma

Authorization of 12 months may be granted for treatment of any of the following indications:

i. HIV-related B-cell lymphoma
ii. Burkitt lymphoma
iii. Castleman's disease
iv. Diffuse large B-cell lymphoma
v. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
vi. Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma
vii. Follicular lymphoma
viii. Mantle cell lymphoma
ix. Marginal zone lymphoma (nodal, extranodal {gastric and non-gastric MALT}, splenic)
x. Post-transplant lymphoproliferative disorder
xi. Pediatric aggressive mature B-cell lymphomas
xii. B-cell lymphoblastic lymphoma
xiii. Primary Mediastinal Large B-Cell Lymphoma

2. **Malignant ascites**
Authorization of 12 months may be granted for treatment of malignant ascites in patients with advanced low-grade non-Hodgkin lymphoma

3. **B-cell acute lymphoblastic leukemia (ALL)**
Authorization of 12 months may be granted for treatment of B-cell ALL.

4. **Chronic lymphocytic leukemia/small lymphocytic lymphoma**
Authorization of 12 months may be granted for treatment of CLL/SLL.

5. **Hairy cell leukemia**
Authorization of 12 months may be granted for treatment of hairy cell leukemia.

6. **Hodgkin's lymphoma**
Authorization of 12 months may be granted for treatment of any of the following indications:
i. Nodular lymphocyte-predominant Hodgkin's lymphoma
ii. CD20-positive relapsed or progressive Hodgkin's lymphoma

7. **Primary cutaneous B-cell lymphoma**
Authorization of 12 months may be granted for treatment of primary cutaneous B-cell lymphoma.

8. **Central nervous system (CNS) cancers**
Authorization of 12 months may be granted for treatment of any of the following indications:
i. Leptomeningeal metastases from lymphomas
ii. Primary CNS lymphoma

9. **Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma**
Authorization of 12 months may be granted for treatment of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma.

10. **Rosai-Dorfman disease**
Authorization of 12 months may be granted for the treatment of Rosai-Dorfman disease.

C. Hematologic indications
Authorization of 12 months may be granted for treatment of any of the following indications:
1. Autoimmune hemolytic anemia
2. Immune or idiopathic thrombocytopenic purpura
3. Thrombotic thrombocytopenic purpura
4. Evans syndrome
5. Acquired factor VIII deficiency (acquired hemophilia A)

D. Multiple sclerosis

Authorization of 12 months may be granted for treatment of relapsing-remitting multiple sclerosis and primary progressive multiple sclerosis.

E. Myasthenia gravis
Authorization of 12 months may be granted for treatment of myasthenia gravis that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

F. Systemic lupus erythematosus
Authorization of 12 months may be granted for treatment of systemic lupus erythematosus that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

G. Granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis
Authorization of 12 months may be granted for treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

H. Sjögren's syndrome
Authorization of 12 months may be granted for treatment of Sjögren's syndrome.

I. Nephrotic syndrome
Authorization of 12 months may be granted for treatment of nephrotic syndrome (e.g., minimal change disease) that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

J. Idiopathic inflammatory myopathy
Authorization of 12 months may be granted for treatment of refractory idiopathic inflammatory myopathy.

K. Immune checkpoint inhibitor-related toxicities
Authorization of 3 months may be granted for treatment of immune checkpoint inhibitor-related toxicities.

L. Lung disease with systemic sclerosis
Authorization of 12 months may be granted for the treatment of lung disease with systemic sclerosis that is refractory to standard therapy (e.g., cyclophosphamide, mycophenolate) or if there is a clinical reason to avoid standard therapy.

M. Thyroid eye disease (moderate to severe)
Authorization of 12 months may be granted for the treatment of moderate to severe thyroid eye disease (excluding patients with risk for dysthyroid optic neuropathy) that is refractory to standard therapy (e.g., IV glucocorticoids) or if there is a clinical reason to avoid standard therapy.

N. Other indications
Authorization of 12 months may be granted for treatment of any of the following indications:
1. Chronic GVHD
2. Prevention of EBV-related PTLD in HSCT recipients
3. Pemphigus vulgaris
4. As part of a non-myeloablative conditioning regimen for allogeneic transplant

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization for 3 months may be granted for the diagnosis of immune checkpoint inhibitor-related toxicities when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The member is receiving benefit from therapy.

B. Authorization for 12 months may be granted for all diagnoses (except immune checkpoint inhibitor-related toxicities) when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat an indication enumerated in Section II.
   3. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Rituxan, Ruxience, Truxima, and Riabni.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Histiocytic neoplasms
4. NCCN Guideline: Hairy cell leukemia
5. NCCN Guideline: Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
6. NCCN Guideline: Hodgkin lymphoma
7. NCCN Guideline: Hematopoietic cell transplantation
8. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO
9. Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anemia
10. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial
11. American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia
12. American Society of Hematology 2019 guidelines for immune thrombocytopenia
13. French recommendations for the management of systemic sclerosis
14. Is rituximab effective for systemic sclerosis? A systematic review and meta-analysis
15. Kidney Disease Improving Global Outcomes (KDIGO) Glomerular Diseases Working Group: KDIGO clinical practice guideline for the management of glomerular diseases
16. Myasthenia gravis: Association of British Neurologists' management guidelines
17. Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care
18. Rituximab effectiveness and safety for treating primary Sjogren's syndrome (pSS): systematic review and meta-analysis
19. Efficacy and safety of rituximab in relapsing-remitting multiple sclerosis: a systematic review and metanalysis
20. Efficacy and safety of different doses and retreatment of rituximab: a randomized, placebo-controlled trial in patients who are biological naïve with active rheumatoid arthritis in an inadequate response to methotrexate (SERENE)
21. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a phase III randomized study (MIRROR)
22. Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus
23. 2019 update of EULAR recommendations for the management of systemic lupus erythematosus
24. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura
25. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with suboptimal response to plasma exchange: experience of the French Thrombotic Microangiopathic Reference Center
26. 2021 European Group on Grave's orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Grave's orbitopathy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rituxan, Ruxience, Truxima and Riabni are covered in addition to the following:
1. B-cell lymphoma
   i. Human Immunodeficiency Virus (HIV) related B-cell lymphoma

ii. Burkitt lymphoma
iii. Castleman's disease
iv. Diffuse large B-cell lymphoma
v. High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
vi. Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma
vii. Follicular lymphoma
viii. Mantle cell lymphoma
ix. Marginal zone lymphoma (nodal, extranodal {gastric and non-gastric mucosa associated lymphoid tissue (MALT) lymphoma}, splenic)
x. Post-transplant lymphoproliferative disorder (PTLD)
xi. Pediatric aggressive mature B-cell lymphomas
xii. B-cell lymphoblastic lymphoma
xiii. Primary Mediastinal Large B-Cell Lymphoma

2. Malignant ascites in advanced low-grade non-Hodgkin lymphoma
3. B-cell acute lymphoblastic leukemia (ALL)
4. CLL/small lymphocytic lymphoma (SLL)
5. Hairy cell leukemia
6. Rosai-Dorfman disease
7. Hodgkin's lymphoma, lymphocyte-predominant
8. Hodgkin's lymphoma, CD20-positive, relapsed or progressive
9. Primary cutaneous B-cell lymphoma
10. Central nervous system (CNS) cancers
    i. Leptomeningeal metastases from lymphomas
    ii. Primary CNS lymphoma
11. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
12. Rheumatoid arthritis, moderate or high disease activity despite disease-modifying anti-rheumatic drug (DMARD) monotherapy
13. Autoimmune hemolytic anemia
14. Immune or idiopathic thrombocytopenic purpura (ITP), as initial therapy
15. Immune or idiopathic thrombocytopenic purpura (ITP), relapsed/refractory to standard therapy (e.g., corticosteroids, immune globulin)
16. Thrombotic thrombocytopenic purpura
17. Relapsing-remitting multiple sclerosis
18. Primary progressive multiple sclerosis
19. Myasthenia gravis, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
20. Systemic lupus erythematosus, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
21. Sjögren's syndrome
22. Chronic graft-versus-host disease (GVHD)
23. Prevention of Epstein-Barr virus (EBV)-related PTLD in hematopoietic stem cell transplant in (HSCT) recipients
24. Evans syndrome
25. Nephrotic syndrome, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
26. Acquired factor VIII deficiency (acquired hemophilia A)
27. Idiopathic inflammatory myopathy, refractory
28. Immune checkpoint inhibitor-related toxicities
29. Allogeneic transplant conditioning
30. Lung disease with systemic sclerosis
31. Thyroid eye disease (moderate to severe)

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the below indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-

cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

1. B-cell lymphomas (human immunodeficiency virus (HIV)-related B-cell lymphoma, Burkitt lymphoma, Castleman's disease, diffuse large B-cell lymphoma, high grade B-cell lymphoma, histological transformation of indolent lymphomas to diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, post-transplant lymphoproliferative disorder, pediatric aggressive mature B-cell lymphomas, B-cell lymphoblastic lymphoma, primary mediastinal large B-cell lymphoma)
2. B-cell acute lymphoblastic leukemia
3. CLL/SLL
4. Hairy cell leukemia
5. Rosai-Dorfman disease
6. Hodgkin's lymphoma, lymphocyte-predominant
7. Hodgkin's lymphoma, CD20-positive, relapsed or progressive
8. Primary cutaneous B-cell lymphoma
9. Leptomeningeal metastases from lymphomas
10. CNS lymphomas
11. Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma

Support for using rituximab to treat malignant ascites in patients with advanced low-grade non-Hodgkin lymphoma can be found in a case report by Ng, Pagliuca and Mufti (2002). The 59-year-old man had achieved partial remission with modified CHOP (cyclophosphamide, doxorubicin, vinblastine, and prednisolone) chemotherapy every 3 weeks for 6 cycles followed by weekly IV rituximab for 4 weeks. Regular drainage of abdominal ascites was still required 8 weeks after IV rituximab. Intraperitoneal rituximab (375 mg/m^2 in 250 mL of 5% dextrose over 4 hours) was administered every 3 days for 4 doses. The treatment was well tolerated, with no reported adverse events or significant changes in blood parameters. An abdominal computed tomography scan 3 weeks after intraperitoneal rituximab showed a marked regression of ascites. No ascites was detected with clinical examination and no additional drainage of ascites was required during the 8-month follow-up period.

Support for using rituximab to rheumatoid arthritis that continues to be of moderate or high disease activity despite DMARD monotherapy can be found in two studies. The addition of rituximab to methotrexate in patients with active rheumatoid arthritis (RA) despite methotrexate treatment significantly improved American College of Rheumatology (ACR)20 and ACR50 response rates at week 24 in the Study Evaluating Rituximab's Efficacy in MTX Inadequate Responders (SERENE), a multicenter, randomized, double-blind, placebo-controlled, phase 3 study (n=509). Eligible patients were 18 to 80 years old, had active RA for at least 6 months despite methotrexate treatment (10 to 25 mg/week) for at least 12 weeks, and had not previously received biological treatment for RA. After a 2-week or longer washout of disease modifying antirheumatic drugs, during which patients continued stable dose methotrexate (10 to 25 mg/week) and folic acid (5 mg/week or greater), patients were randomized to IV therapy on days 1 and 15 with rituximab 500 mg (2 x500 group; n=167), rituximab 1000 mg (2 x 1000 group; n=170), or placebo (n=172); premedication for all 3 groups was methylprednisolone 100 mg IV. NSAIDs and stable dose corticosteroids (prednisolone less than or equal to 10 mg/day orally (or equivalent)) were allowed. Patients who were not in remission at week 24 (Disease Activity Score (28 joints)-erythrocyte sedimentation rate (DAS28-ESR) less than 2.6) and met safety criteria were eligible for open-label rituximab treatment with the randomized dose (or 2 doses of 500 mg for initial placebo assignment). Initiation of 1 non-biologic DMARD was allowed if a less than 20% improvement in tender joint count (JC) and swollen (JC) versus baseline was noted between weeks 16 and 23. At week 24, significantly more patients in the rituximab 2 x500 mg and rituximab 2 x 1000 mg groups than in the placebo group, respectively, achieved an ACR20 response (primary outcome; 54.5% and 50.6% vs 23.3%) and an ACR 50 response (26.3% and 25.9% vs 9.3%). In the rituximab 2 x 500 mg and rituximab 2 x 1000 mg groups compared with the placebo group, respectively, there were also significant improvements in clinical remission (9.6% and 9.4% vs 2.3%), European League Against Rheumatism (EULAR) good response (17.4% and 11.8% vs 4.7%), and EULAR moderate response (49.1% and 51.2% vs 29.1%). By week 48, 93.5% of the rituximab 2 x 500 mg group, 91.3% of the rituximab 2 x 1000 mg group, and 89.5% of the placebo group had received a second course of treatment. At week 48, levels of disease activity were maintained or improved, with ACR20 response rates at 55.7% for rituximab 2 x 500 mg and 57.6% for rituximab 2 x 1000 mg and ACR50 response rates at 32.9% and 34.1%, respectively. Adverse effects to week 24 were reported in 77% of the rituximab 2 x 500 mg group, 76% of the rituximab 2 x 1000 mg group, and 74% of the placebo group, and included infusion-related reactions with the day 1 infusion (19%, 25%, and 14%) and with the day 15 infusion

(7%, 6%, and 8%). The overall infection rate per 100 patient-years was 138.13 in the rituximab 500 mg group, 120.45 in the rituximab 1000 mg group, and 159 in the placebo group with a serious infection rate of 1.26, 2.46, and 8.83, respectively. Adverse effects to 48 weeks with rituximab 2 x 500 mg and rituximab 2 x 1000 mg were similar to the rates at 24 weeks.
An American College of Rheumatology (ACR)20 response was achieved in 64% to 72% of patients with rheumatoid arthritis (RA) at 48 weeks after treatment with 1 of 3 rituximab regimens administered initially and at 24 weeks plus methotrexate, in the multicenter, randomized, double-blind, phase 3 MIRROR trial (n=346). Eligible patients had a diagnosis of RA for at least 6 months, had active disease despite methotrexate therapy (10 to 25 mg/week) for at least 12 weeks (stable dose for at least 4 weeks), and had previously received no more than 1 biological agent for RA. Patients continued stable methotrexate doses of 10 to 25 mg/week during the study and were randomized to 1 of 3 rituximab regimens: 2 x 500 mg group, who received two 500 mg doses initially and at week 24 (n=134; mean age, 53.6 years); dose escalation group, who received two 500 mg doses initially and two 1000 mg doses at week 24 (n=119; mean age, 52.3 years); and 2 x 1000 mg group, who received two 1000 mg doses initially and at week 24 (n=93; mean age 51.3 years). Methylprednisolone 100 mg IV was administered before all rituximab infusions. Folic acid (5 mg/week), NSAIDs, oral glucocorticoids (10 mg/day or less), and intra-articular glucocorticoid injections of no more than 1 joint per 24 weeks were allowed; additional nonbiological and biological disease modifying antirheumatic drugs were not allowed. ACR20 response rates at 48 weeks were not significantly different between the rituximab 2 x 500 mg group and the dose escalation group (primary outcome; 64% for both groups) or between the rituximab 2 x 500 mg group and the rituximab 2 x 1000 mg group (64% vs 72%). ACR20 response rates at 48 weeks were similar in patients who had received a previous biological agent and patients who had not (65% and 67%, respectively). There were no significant differences among the 2 x 500 mg group, the dose escalation group, and the 2 x 1000 mg group, respectively, at 48 weeks in ACR50 response rates (39%, 39%, and 48%) or ACR70 response rates (20%, 19%, 23%). A moderate or good European League Against Rheumatism (EULAR) response was achieved by significantly more patients in the rituximab 2 x 1000 mg group than in the rituximab 2 x 500 mg group (89% vs 73%) or the dose escalation group (89% vs 72%). Disease Activity Score (28 joints)-erythrocyte sedimentation rate (DAS28-ESR) remission (DAS28-ESR less than 2.6) was achieved by 9% in the rituximab 2 x 500 mg group, by 13% in the dose escalation group, and by 19% in the rituximab 2 x 1000 mg group. Adverse effects were similar in all 3 treatment groups, occurred in 89% to 91% of patients, and included infusion-related reactions (30% to 39%) and infections (56% to 65%).

Jager et al supports using rituximab in the treatment of autoimmune hemolytic anemia. In patients with symptomatic, primary cold agglutinin disease, first-line treatment consists of rituximab alone, or rituximab plus bendamustine in fit patients. Rituximab plus bendamustine should be given if not previously used, or in patients who responded to it as first-line therapy and at least 2 years have passed since treatment. Rituximab monotherapy may be repeated in patients who previously responded for at least 1 year. Rituximab plus fludarabine is an option for fit, elderly patients. Corticosteroids remain first-line therapy for warm-AIHA, while the addition of rituximab should be considered early in severe cases and if no prompt response to steroids is achieved.
A systematic review by Liu et al identified 2 randomized studies of rituximab in patients with newly-diagnosed warm autoimmune hemolytic anemia. The addition of rituximab to a glucocorticoid significantly increased the likelihood of a complete hematological response at 12 months compared with glucocorticoid alone, but there were no significant improvements on the likelihood of a complete response at 6 months, partial responses at 6 or 12 months, or red blood cell requirement at 2, 6, or 12 months.

Support for using rituximab to treat immune thrombocytopenia is supported in treatment guidelines. The American Society of Hematology has published guidelines on the treatment of immune thrombocytopenia (Neunert et al). Rituximab may be considered in patients who have failed first-line therapy with conventional doses of corticosteroids, IV immune globulin, or splenectomy and who are at risk of bleeding. In 19 reports, the pooled estimate of overall platelet count response in 313 patients was 62.5%; however, durability of response varied. In 1 study of 306 patients, severe or life-threatening complications associated with rituximab occurred in 3.3%. Rituximab may be considered in patients with ITP who continue to have significant bleeding despite first-line therapy with corticosteroids or IV immune globulin.
As initial treatment of newly diagnosed ITP, corticosteroids alone rather than corticosteroids with rituximab is suggested (evidence with very low certainty). An initial course of corticosteroids with rituximab may be preferred if the potential for remission is valued higher than the potential for adverse events with rituximab. Rituximab may also be considered as an alternative to splenectomy in patients with chronic ITP and in those who respond poorly to splenectomy. In 1 study, only 8 of 36 patients maintained platelet counts greater than 50 x 10^9/L at the 1-year follow-up after weekly doses of rituximab; however, other studies have demonstrated

higher response rates, particularly when the rituximab dose was doubled after lack of response. Serum sickness was reported in some patients.

Froissart et al for the French Thrombotic Microangiopathies Reference Center, supports using rituximab for thrombotic thrombocytopenic purpura. The time to a durable remission was significantly shorter in patients with thrombotic thrombocytopenic purpura (TTP) who had a suboptimal response to therapeutic plasma exchange (TPE) and received rituximab compared with historical controls who did not receive rituximab; however, the mean plasma volume required to achieve durable remission did not differ significantly between the 2 groups in a prospective cohort study (n=74). Patients with thrombotic microangiopathy (Coombs-negative microangiopathic hemolytic anemia, acute peripheral thrombocytopenia [platelet count less than 150 x 10^9/L], and absence of identifiable cause for thrombocytopenia and microangiopathic hemolytic anemia) and mild renal involvement (less than 2.26 mg/dL) were diagnosed with TTP, with a definitive diagnosis confirmed by ADAMTS13 activity of less than 10%. Patients with hemolytic uremic syndrome, rituximab therapy for a previous TTP episode, or detectable ADAMTS13 activity after rituximab therapy were excluded. Patients with a suboptimal response to daily TPE (plasma volume, 1.5 predicted plasma volume for first procedure, 1 times predicted plasma volume thereafter until remission, followed by maintenance TPE tapered over 3 weeks) received rituximab 375 mg/m^2 on the day of diagnosis of suboptimal response (day 0), day 3, day 7, and day 14 with premedication of dexchlorpheniramine 10 mg IV and acetaminophen 1 g IV. Patients without active infection received glucocorticoid therapy (1 mg/kg/day) for 3 weeks; patients not receiving glucocorticoids received methylprednisolone 30 mg IV. Suboptimal response was defined as an exacerbation (worsening neurologic manifestations, platelet count of less than 100 x 10^9/L for at least 2 days, or platelet count decrease of more than one-third the highest count for at least 2 days) or TTP refractory to TPE (platelet count after 4 days of TPE less than 2 times baseline with LDH persistently greater than ULN). Durable remission was defined as complete response (resolution of neurologic manifestations and platelet count greater than 150 x 10^9/L for at least 2 days) with no thrombocytopenia or clinical worsening during at least 30 days after first day of platelet recovery (including time on maintenance TPE). In the rituximab group (n=21; mean age, 36.8 +/- 11 years; glucocorticoid therapy, 71%; cytotoxic therapy, 0%; mean follow-up, 33 +/- 17.4 months) compared with historical controls (n=53; mean age, 41.7 +/- 16 years; glucocorticoid therapy, 79%; vincristine, n=17; vincristine and cyclophosphamide, n=3; mean follow-up, 35.3 +/- 28.5 months), platelet count recovery time (coprimary outcome) was significantly shorter (p=0.03). At day 35, significantly more patients (100% vs 78%; p less than 0.02) had achieved a durable remission; durable remission was achieved at a mean of 12 +/- 6.7 days after rituximab initiation. There were no significant differences between the rituximab group and the historical controls in mean plasma volume required to achieve a durable remission (coprimary outcome; 891 +/- 402 vs 999 +/- 583 mL/kg; p=0.67), exacerbation rate (2 of 21 vs 16 of 53; p less than 0.08), or relapse rate (within first year, 0% vs 9.4% [p=0.34]; after first year, 15.8% vs not reported [p=0.68]). In the rituximab group, mean peripheral B-cell counts were decreased by 80% compared with baseline on day 4; decreased to 1% of baseline by day 8; undetectable at month 3; less than 5% of baseline after 3 and 6 months; and greater than 10% of baseline after 12 months. In an analysis of the rituximab group (n=21) compared with historical controls with available data (n=19), ADAMTS13 activity was significantly higher after 1, 3, 6, and 9 months, but was similar at 12 months, and ADAMTS13 antibody titers were significantly lower at 3, 6, and 9 months and similar at 12 months. No severe adverse effects, hypogammaglobulinemia, or clinically relevant infections were reported with rituximab.

Support for using rituximab to treat multiple sclerosis can be found in two randomized trials.
A randomized, controlled trial and systematic review support using rituximab to treat relapsing-remitting multiple sclerosis. Svenningsson et al found rituximab therapy significantly reduced risk of relapse at 24 months compared with dimethyl fumarate in adults with treatment-naive relapsing remitting multiple sclerosis in the randomized, phase 3 RIFUND-MS trial. Toxicity was consistent with known safety profiles of each agent. In a systematic review and meta-analysis by Tian et al in patients with relapsing-remitting multiple sclerosis, rituximab significantly reduced both the annualized relapse rate and the functional burden of disease, as measured by the mean Expanded Disability Status Scale score. Relapse rates declined over duration of rituximab use but remained at less than 15% through 96 weeks. This compilation of studies is inclusive, down to reports of 10 or more patients, but methodological quality and overall heterogeneity of the studies may limit these findings.
Support for using rituximab for primary progressive multiple sclerosis can be found in a randomized trial of patients with a disease duration of at least one year (N=439) by Hawker et al. There was no significant difference in rate of confirmed disease progression (CDP) between rituximab (30.2%) and placebo (38.5%) at 96 weeks. However, patients receiving rituximab did experience significantly smaller increases in median T2 lesion volume compared with those receiving placebo (301.95 mm^3 vs 809.5 mm^3). Subgroup analyses

demonstrated that time to CDP was significantly delayed with the administration of rituximab in patients younger than 51 years of age (HR, 0.52) and in those with gadolinium brain lesions at baseline (HR, 0.41). Additionally, patients less than 51 years of age with baseline gadolinium lesions experienced a 61.6% relative reduction in total T2 lesion volume accumulation with rituximab compared with 50.7% for patients 51 years or older with baseline gadolinium lesions. In an exploratory analysis the median increase from baseline to week 96 in the Multiple Sclerosis Functional Composite (MSFC) timed 25-foot walk was 0.9 seconds with rituximab versus 1.48 seconds with placebo. Safety follow-up through 122 weeks demonstrated that the incidence of adverse events was similar between treatment groups; mild to moderate infusion-related reactions were more common with rituximab but the incidence decreased with successive infusions.

Support for using rituximab to treat myasthenia gravis (MG) can be found in one published guideline and a large meta-analysis. According to the Association of British Neurologists, rituximab has a role in managing poorly responsive myasthenia gravis when treatment with azathioprine has failed or the patient cannot tolerate it.
Zhao and colleagues (2021) noted that MG is an autoimmune neuromuscular disease. Nearly 10 to 30% of patients with MG are refractory to conventional therapy; rituximab is increasingly used in autoimmune disorders. In a systematic review and meta-analysis, these researchers examined the safety and effectiveness of rituximab for the treatment of refractory MG. Studies published between January 1, 2000 and January 17, 2021 were searched in PubMed, Embase, Cochrane Library, and ClincalTrails.gov. Primary outcomes included proportion of patients achieving minimal manifestation status (MMS) or better and quantitative MG (QMG) score change from baseline. Secondary outcomes were glucocorticoids (GC) doses change from baseline and proportion of patients discontinuing oral immunosuppressants. A total of 24 studies involving 417 patients were included in the meta-analysis. An overall 64 % (95 % CI: 49 % to 77 %) of patients achieved MMS or better. The estimated reduction of QMG score was 1.55 (95 % CI: 0.88 to 2.22). The mean reduction of GC doses was 1.46 (95 % CI: 1.10 to 1.82). The proportion of patients discontinuing oral immunosuppressants was 81 % (95 % CI: 66 % to 93 %). Subgroup analyses showed that the proportion of patients achieving MMS or better and discontinuing oral immunosuppressants was higher in MuSK-MG group than those in AChR-MG group. Improvement was more pronounced in patients with mild-to-moderate MG compared to those with severe MG. Moreover, the effectiveness appeared to be independent of the dose of rituximab. A total of 19.6% of patients experienced AEs, most of which were mild-to-moderate. Only 1 patient developed PML. The authors concluded that this systemic review and meta-analysis suggested that rituximab therapy could improve the PIS of a considerable number of patients with refractory MG to reach MMS or better with a good safety profile. It also exhibited a steroid-sparing effect. Furthermore, rituximab reduced QMG scores and the use of conventional oral immunosuppressants. The effectiveness was related to the patient's serotype and disease severity, but not to the doses of rituximab. These researchers stated that randomized controlled trials are needed to examine the effectiveness of rituximab in the treatment of refractory MG and to identify the characteristics of patients who might respond well to rituximab.

The authors stated that this study had several drawbacks. First, most of the studies included in the meta-analysis were observational studies, which might over-estimate the effectiveness of treatments compared with controlled trials. Second, these researchers could not compare the effectiveness of rituximab with other drugs since most of the included studies were single-arm. Third, the number of patients in each study was relatively small. In subgroup analysis, the number of cases in some studies was no more than 5, which resulted in great randomness of research results. Finally, the heterogeneity between studies was remarkable. There were many reasons for the high heterogeneity. Myasthenia gravis is a rare disease with high heterogeneity. Moreover, the rituximab regimen, follow-up duration and baseline characteristics of patients differed among studies. These investigators could not carry out meta-regression because some information was inaccessible in studies.

Support for using rituximab for systemic lupus erythematosus can be found in treatment guidelines. The European League Against Rheumatism (EULAR) recommendations for the management of systemic lupus erythematosus recommend rituximab as a treatment option for patients with organ-threatening SLE that is refractory to, or in patients with intolerance or contraindications to immunosuppressive agents. Additionally, a systematic review by Cobo-Ibanez et al found rituximab was safe and effective in patients with non-renal systemic lupus erythematosus, specifically disease activity, arthritis, thrombocytopenia, anti-dsDNA, and steroids-paring effect; long-term studies are needed.

Support for using rituximab for primary Sjogren's syndrome can be found in a published systematic review. Souza et al completed a systematic review and meta-analysis to review the literature available addressing

using rituximab for primary Sjogren's syndrome. Four 24-week randomized trials in 276 adults with primary Sjogren syndrome, a single course of rituximab 1 g IV on days 1 and 15 compared with placebo significantly improved lacrimal gland function using the lissamine green test (1 study), but no significant between-group difference using the Schirmer test (2 studies). Rituximab was associated with significant improvement in the salivary flow rate (low-quality evidence, 3 studies), but no significant difference in a 30% improvement in fatigue (3 studies), quality of life improvement (3 studies), or disease activity (2 studies). There was no significant between-group difference in serious adverse events.

Support for using rituximab for prophylaxis against Epstein-Barr virus disease in patients who have received a hematopoietic stem cell transplant can be found in a guideline published by Tomblyn et al. To prevent EBV-associated PTLD, high-risk patients (e.g., after T cell depletion, use of anti-T cell antibodies, umbilical cord blood transplants, and haplo identical transplants) should be assessed for EBV DNA load using a EBV PCR assay. Monitoring allows for preemptive immunosuppression reduction if feasible. If no response occurs with immunosuppression reduction, preemptive therapy with rituximab is recommended to prevent PTLD. Infusion of donor-derived, EBV-specific cytotoxic T-lymphocytes has shown some efficacy in the prophylaxis of EBV-lymphoma among recipients of T cell-depleted unrelated or mismatched allogeneic recipients. Other treatments that have been used include expanded donor-derived EBV-specific T cells to control blood EBV DNA levels and use of B cell depletion to decrease the risk of EBV PTLD. Due to lack of efficacy, prophylaxis or preemptive treatment with currently available antiviral agents is not recommended.

Support for using rituximab for Evan syndrome can be found in a guideline, small trials and a case report. The British Society for Haematology supports using rituximab as second-line therapy for primary Evans syndrome. Other second-line therapies include immunosuppressive drugs, danazol, splenectomy or vincristine. Rituximab appears to effectively treat pediatric patients with refractory Evans syndrome based upon small, prospective, single-arm trials and case reports; however, long-term, randomized, controlled, clinical trials are not available to confirm safety in this population. Two prospective studies, one of severe immune thrombocytopenic purpura and one of autoimmune hemolytic anemia, contained subgroups of Evans patients who responded to treatment with rituximab based upon hematologic results from the entire cohort. Three Evans patients relapsed and were successfully retreated with rituximab. Safety data are inconclusive since adverse events (i.e., infusion reactions, bleeding, and serum sickness) were reported for the entire cohort, and it is unclear which of these occurred in the Evans subpopulation. Varicella infection requiring hospitalization was reported in one Evans syndrome patient after rituximab treatment. During post marketing surveillance, it has been reported that two adult patients died from progressive multifocal leukoencephalopathy (PML) while receiving rituximab for another autoimmune disease, systemic lupus erythematosus. PML was caused by reactivation of JC virus, and risk in the pediatric population is unknown.

Support for using rituximab for the treatment of nephrotic syndrome can be found in the KDIGO glomerular disease working group. In patients with frequently relapsing steroid-dependent minimal change disease, treatment with cyclophosphamide, rituximab, calcineurin inhibitors (cyclosporine, tacrolimus), or mycophenolic acid analogues (mycophenolate mofetil, sodium mycophenolate) is recommended rather than prednisone alone or no treatment. Rituximab has been associated with inducing remission in 65% to 100% of patients and has reduced the number of relapses, and the number of immunosuppressive drugs. However, the long-term efficacy and risks are unknown.

Support for using rituximab for acquired factor VIII deficiency (acquired hemophilia A) can be found in guidelines from UKHCDO. Rituximab can be considered as first-line therapy if standard immunosuppression is contraindicated but may have limited efficacy if used as a single agent. If there is no response within 3–5 weeks, second-line therapies should be considered. The most common second-line treatment is with rituximab combined with other agents. Alternative options are calcineurin inhibitors, multiple immunosuppressive agents and immune tolerance protocols.

Support for using rituximab for idiopathic inflammatory myopathy can be found in a randomized trial. Treatment with rituximab resulted in an 83% total rate of improvement and provided steroid-sparing effects after 44 weeks, despite not showing a difference between the randomized groups of "early" versus "late" rituximab administration in 195 evaluable patients with muscle weakness due to refractory polymyositis (n=76), dermatomyositis (n=76), or juvenile dermatomyositis (n=48) in the Rituximab in Myositis (RIM) trial. Improvement was defined as at least a 20% improvement in 3 of any 6 core set measures (CSM) plus no more than 2 CSMs worsening by more than 25% (excluding muscle manual testing [MMT]). The 6 CSMs consisted of MMT using the MMT-8 measure, patient global visual analog scale (VAS), physician global VAS, Health

Assessment Questionnaire disability index, muscle enzymes, and global extramuscular disease activity score. The time to achieve the preliminary International Myositis Assessment and Clinical Studies Group definition of improvement was 20 weeks in patients who received "early" rituximab (at weeks 0 and 1, followed by placebo at weeks 8 and 9) compared with 20.2 weeks in patients who received "late" rituximab (at weeks 8 and 9, with placebo at weeks 0 and 1). At 8 weeks, 15% of the rituximab group and 20.6% of the placebo group had met the definition of improvement. In 160 patients receiving a mean of 20.8 mg/day of prednisone at baseline, the mean dosage significantly decreased to 14.4 mg/day at the end of the trial. Of the 17 patients with worsening disease after initial improvement, 9 were retreated with rituximab and 8 of these met the definition of improvement after 19.9 weeks. Infections were the most common serious adverse event, particularly pneumonia (n=6) and cellulitis (n=6). Infusion reactions were significantly more common with rituximab than placebo (15.4% vs 5.3%), with 4 severe reactions and 2 hospitalizations. Glucocorticoids were not administered as premedications. Rituximab was administered in adults at a dosage of 750 mg/m^2/dose up to 1000 mg/dose IV for 2 doses given 1 week apart. Patients were also receiving stables doses of glucocorticoids and at least one other immunosuppressant.

Support for rituximab as a treatment for systemic sclerosis-associated interstitial lung disease can be found in a guideline and meta-analysis. Hachulla et al indicated rituximab may be considered as a third-line treatment option in patients with systemic sclerosis-associated interstitial lung disease who have failed cyclophosphamide and/or mycophenolate. A meta-analysis by de Figueriredo Caldas et al found rituximab significantly improved lung function, but not skin fibrosis, in adults with systemic sclerosis. A systematic review that included the 3 studies from the meta-analysis (90 patients) plus 7 nonrandomized studies (128 patients) reported mixed results.

Support for using rituximab to treat thyroid eye disease is supported by a European guideline. The European Group on Grave's orbitopathy (EUGOGO) indicate rituximab may be used as a second-line treatment for moderate to severe and active Graves' orbitopathy of recent onset (less than 12 months) if refractory to IV glucocorticoids, excluding patients with risk for dysthyroid optic neuropathy. This recommendation is based on two small, randomized double-blind, conflicting trials that differ in final treatment dosage.

Support for using rituximab for chronic graft versus host disease (cGVHD) can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using rituximab as conditioning for allogenic transplant can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as conditioning for allogenic transplant as part of a non-myeloablative regimen in combination with cyclophosphamide and fludarabine.

Support for using rituximab for the management of immunotherapy-related toxicities can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as additional therapy for moderate (G2), severe (G3), or life-threatening (G4) immunotherapy-related bullous dermatitis. The guideline also supports the use of rituximab for moderate, severe, or life-threatening steroid-refractory myositis (proximal muscle weakness, neck flexor weakness, with or without myalgias) for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids. Additionally, rituximab may be used as additional therapy for severe (G3-4) myasthenia gravis in patients refractory to plasmapheresis or intravenous immune globulin (IVIG). Finally, rituximab can be used for encephalitis in patients positive for autoimmune encephalopathy antibody, or who have limited or no improvement after 7 to 14 days on high-dose corticosteroids with or without IVIG.

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RIVFLOZA (nedosiran)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Rivfloza is indicated to lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function, e.g., eGFR of greater than or equal to 30 mL/min/1.73 m^2

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Molecular genetic test results demonstrating a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene or liver enzyme analysis results demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity.
B. Chart notes or medical records demonstrating a positive response to therapy (for continuation requests).

III. CRITERIA FOR INITIAL APPROVAL

Primary hyperoxaluria type 1 (PH1)
Authorization of 12 months may be granted for the treatment of primary hyperoxaluria type 1 (PH1) when all of the following criteria are met:
A. Member is 9 years of age or older.
B. Member has a diagnosis of PH1 confirmed by either of the following:
    1. Molecular genetic test results demonstrating a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene.
    2. Liver enzyme analysis results demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity.
C. Member has relatively preserved kidney function (e.g., eGFR of greater than or equal to 30 mL/min/1.73 m^2).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Rivfloza.
B. Rivfloza is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., decrease or normalization of urinary and/or plasma oxalate levels, improvement in kidney function).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Rivfloza.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rivfloza are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Rivfloza [package insert]. Lexington, MA: Dicerna Pharmaceuticals, Inc.; October 2023.
2. Niaudet, P. Primary hyperoxaluria. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022.
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ROCTAVIAN (valoctocogene roxaparvovec-rvox)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Roctavian is indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without antibodies to adeno-associated virus serotype 5 (AAV5) detected by an FDA-approved test.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Chart notes, medical records, or lab results documenting all of the following:
A. Severe factor VIII deficiency (factor VIII activity levels less than or equal to 1 IU/dL).
B. Absence of pre-existing antibodies to the adeno-associated virus serotype 5 (AAV5) capsid.
C. Absence of factor VIII inhibitor confirmed by a Bethesda assay (lab test results required).

III. PRESCRIBER SPECIALTIES

Treatment should be under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders.

IV. CRITERIA FOR INITIAL APPROVAL

Hemophilia A
Authorization of 3 months for one dose total may be granted for treatment of severe hemophilia A when all of the following criteria are met:
A. Member must be 18 years of age or older.
B. Member has severe disease with factor VIII activity levels less than or equal to 1 IU/dL.
C. Absence of pre-existing antibodies to AAV5 was confirmed by an FDA-approved test (e.g., AAV5 Detect CDx™).
D. Member does not have prior or active factor VIII inhibitors (inhibitor titer must be less than 0.6 Bethesda Units [BU]).
E. Member has not received treatment with the requested medication previously.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Roctavian.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs

e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Roctavian are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Roctavian [package insert]. Novato, CA: BioMarin Pharmaceutical Inc.; June 2023.

ROLVEDON (eflapegrastim-xnst)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Rolvedon is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia.

B. Compendial Uses
1. Stem cell transplantation-related indications
2. Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
3. Hematopoietic acute radiation syndrome
4. Hairy cell leukemia, neutropenic fever

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Primary Prophylaxis of Febrile Neutropenia
Documentation of the member's diagnosis and chemotherapeutic regimen.

III. CRITERIA FOR INITIAL APPROVAL

A. Prevention of neutropenia in cancer patients receiving myelosuppressive chemotherapy
Authorization of 6 months may be granted for prevention of febrile neutropenia for members with solid tumors or non-myeloid malignancies when the requested medication will not be administered with weekly chemotherapy regimens and the member will not be receiving chemotherapy at the same time as they receive radiation therapy.

B. Other indications
Authorization of 6 months may be granted for members with any of the following indications:
1. Stem cell transplantation-related indications
2. Hematopoietic subsyndrome of acute radiation syndrome
3. Hairy cell leukemia with neutropenic fever following chemotherapy

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Rolvedon.

2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Hairy cell leukemia
4. NCCN Guideline: Hematopoietic growth factors
5. NCCN Guideline: Hematopoietic cell transplantation

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rolvedon are covered in addition to the following:

1. Stem cell transplantation-related indications
2. Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
3. Hematopoietic acute radiation syndrome
4. Hairy cell leukemia, neutropenic fever

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Rolvedon for stem cell transplantation-related indications can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of G-CSF as treatment for hematopoietic cell mobilization for autologous donors in combination with plerixafor.

Support for using Rolvedon as prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors. The NCCN Guideline supports the use of Rolvedon for prophylaxis of chemotherapy-induced febrile neutropenia or other dose limiting neutropenic events in high-risk, intermediate-risk and low-risk patients with solid tumors.

Support for using Rolvedon to treat hematopoietic acute radiation syndrome can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors. The NCCN Guideline for hematopoietic growth factors supports the use of G-CSF in patients with radiation-induced myelosuppression following a radiologic/nuclear incident.

Support for using Rolvedon in hairy cell leukemia for neutropenic fever in a patient being treated for hairy cell leukemia can be found in the National Comprehensive Cancer Network's guideline for hairy cell leukemia. The NCCN Guideline for hairy cell leukemia supports using neutrophil growth factors for patients with neutropenic fever following systemic therapy.

VII. REFERENCES

1. Rolvedon [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; September 2022.
2. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
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4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf Accessed June 13, 2023.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hairy Cell Leukemia. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf Accessed June 19, 2023.

RUCONEST (C1 esterase inhibitor [recombinant])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Ruconest is indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial authorization:
   1. C1 inhibitor functional and antigenic protein levels
   2. F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
   3. Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
B. For continuation of therapy, chart notes demonstrating a reduction in severity and/or duration of attacks

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

IV. CRITERIA FOR INITIAL APPROVAL

Hereditary angioedema (HAE)
Authorization of 6 months may be granted for treatment of acute HAE attacks when either of the following criteria are met at the time of diagnosis:
A. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
   1. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
   2. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
B. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
   1. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
   2. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment of acute HAE attacks when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The member is receiving benefit from therapy. Benefit is defined as a reduction in severity and/or duration of acute attacks.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Ruconest.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.
4. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
5. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
6. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.
7. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
8. International consensus on hereditary and acquired angioedema.
9. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.
10. Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ruconest are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.
When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines.

There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

VIII. REFERENCES

1. Ruconest [package insert]. Warren, NJ: Pharming Healthcare Inc.; April 2020.
2. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010;6(1):24.
3. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*. 2012;67:147-157.
4. Busse PJ, Christiansen, SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol: In Practice.* 2021 Jan;9(1):132-150.e3.
5. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc*. 2012;33(6):S145-S156.
6. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update. *Allergy*. 2022 Jan 10. doi: 10.1111/all. 15214. Online ahead of print.
7. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109:395-202.
8. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69:602-616.
9. Bowen T. Hereditary angioedema: beyond international consensus – circa December 2010 – The Canadian Society of Allergy and Clinical Immunology Dr. David McCourtie Lecture. *Allergy Asthma Clin Immunol*. 2011;7(1):1.
10. Bernstein JA. Update on angioedema: Evaluation, diagnosis, and treatment. *Allergy and Asthma Proceedings.* 2011;32(6):408-412.
11. Longhurst H, Cicardi M. Hereditary angio-edema. *Lancet.* 2012;379:474-481.
12. Veronez CL, Csuka D, Sheik FR, et al. The expanding spectrum of mutations in hereditary angioedema. *J Allergy Clin Immunol Pract.* 2021;S2213-2198(21)00312-3.

RYBREVANT (amivantamab-vmjw)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Rybrevant is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

B. Compendial Use
Recurrent, advanced, or metastatic EGFR exon 20 insertion mutation positive NSCLC

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all initial requests: Test results showing the presence of EGFR exon 20 insertion mutations**.**

III. CRITERIA FOR INITIAL APPROVAL

Non-small cell lung cancer (NSCLC)
Authorization of 12 months may be granted for treatment of advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy, when used as a single agent.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen and
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Rybrevant.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Non-small cell lung cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rybrevant are covered including recurrent, advanced, or metastatic EGFR exon 20 mutation positive NSCLC.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Rybrevant to treat recurrent, advanced, or metastatic EGFR exon 20 mutation positive NSCLC can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Rybrevant [package insert]. Horsham, PA: Janssen Biotech, Inc.; November 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed March 1, 2023.

RYLAZE (asparaginase erwinia chrysanthemi (recombinant)-rywn)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Rylaze is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

B. Compendial Uses
Extranodal Natural Killer/T-cell lymphoma/ Aggressive NK-cell Leukemia (ANKL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LBL)
Authorization of 12 months may be granted for treatment of ALL or LBL in members 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase (e.g., pegaspargase) and the requested medication will be used in conjunction with multi-agent chemotherapy.

B. Extranodal Natural Killer/T-cell Lymphoma / Aggressive NK-cell Leukemia (ANKL)
Authorization of 12 months may be granted for treatment of ENKL or ANKL when both of the following criteria are met:
1. The member has previously received and developed hypersensitivity to an E. coli-derived asparaginase (e.g., pegaspargase).
2. The requested medication is used in conjunction with multi-agent chemotherapy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen and
    2. No evidence of disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Rylaze.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Acute lymphoblastic leukemia
4. NCCN Guideline: T-cell lymphomas
5. NCCN Guideline: Pediatric acute lymphoblastic leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rylaze are covered in addition to extranodal Natural Killer/T-cell lymphoma/ Aggressive NK-cell Leukemia (ANKL).

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Rylaze to treat ALL, LBL, and extranodal natural killer/T-cell lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Rylaze to treat extranodal natural killer/T-cell lymphoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Rylaze [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; November 2022.
2. The NCCN Drugs & Biologics Compendium® ©2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed May 31, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: T-Cell Lymphomas. Version 1.2023. https:// www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed May 31, 2023.
4. Rylaze. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed May 31, 2023.

RYPLAZIM (plasminogen, human-tvmh)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Ryplazim is plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial Requests: Medical records (e.g., chart notes, lab reports) documenting a baseline plasminogen activity level and a history of lesions and symptoms consistent with diagnosis.
B. Continuation Requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

III. CRITERIA FOR INITIAL APPROVAL

Plasminogen deficiency type 1 (hypoplasminogenemia)
Authorization of 12 months may be granted for treatment of plasminogen deficiency type 1 (hypoplasminogenemia) when all of the following criteria are met:
A. Member has a baseline plasminogen activity level of 45% or less.
B. Member has a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 (e.g., ligneous conjunctivitis, ligneous gingivitis or gingival overgrowth, vision abnormalities, respiratory distress and/or obstruction, abnormal wound healing).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. Disease stability while on the current regimen or
    2. Disease improvement (e.g., improvement lesion number and/or size, absence of new lesion development, improvement in respiratory function, increased quality of life) while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Ryplazim.

2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ryplazim are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Ryplazim [package insert]. Fort Lee, NJ: Prometic Biotherapeutics Inc.; June 2023.
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3. Celkan T. Plasminogen deficiency. *J Thromb Thrombolysis.* January 2017; 43(1):132-138.

RYSTIGGO (rozanolixizumab-noli)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Rystiggo is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests: chart notes, medical records, or claims history documenting:
   1. Positive anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody test
   2. Myasthenia Gravis Foundation of America (MGFA) clinical classification score
   3. MG activities of daily living (MG-ADL) score
   4. Use of an acetylcholinesterase (AChE) inhibitor, steroid, or non-steroidal immunosuppressive therapy (NSIST)
B. For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

III. CRITERIA FOR INITIAL APPROVAL

Generalized myasthenia gravis (gMG)
Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:
1. Anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive
2. Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IVa
3. MG activities of daily living (MG-ADL) total score of 3 or more with at least 3 points from non-ocular symptoms
4. On a stable dose of at least one of the following:
   a. Acetylcholinesterase inhibitors (e.g., pyridostigmine)
   b. Steroids (at least 1 month of treatment)
   c. Nonsteroidal immunosuppressive therapy (NSIST) (at least 6 months of treatment) (e.g., azathioprine, mycophenolate mofetil)

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Rystiggo.
2. Rystiggo is being used to treat an indication enumerated in Section III.

3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity or disease progression while on the current regimen, AND
   b. The member demonstrates a positive response to therapy (e.g., improvement in MG-ADL score, changes compared to baseline in Quantitative Myasthenia Gravis (QMG) total score).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Rystiggo.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. International consensus guidance for management of myasthenia gravis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rystiggo are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Rystiggo [package insert]. Smyrna, GA: UCB, Inc.; June 2023.
2. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2021; 96 (3) 114-122.
3. Bril V, Drużdż A, Grosskreutz J, et al. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. Lancet Neurol. 2023;22(5):383-394.

SANDOSTATIN LAR (octreotide acetate for injectable suspension)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Sandostatin LAR Depot is indicated in patients who have responded to and tolerated Sandostatin subcutaneous injection for:
1. Long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.
2. Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
3. Long-term treatment of the profuse watery diarrhea associated with vasoactive intestinal peptide (VIP)-secreting tumors.

B. Compendial Uses
1. Neuroendocrine tumors (NETs)
   a. NETs of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors)
   b. NETs of the pancreas (islet cell tumors)
   c. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
2. Pheochromocytoma/paraganglioma
3. Meningiomas
4. Thymomas and thymic carcinomas
5. Bowel obstruction due to peritoneal carcinomatosis
6. Postgastrectomy dumping syndrome
7. Hepatocellular carcinoma
8. Zollinger-Ellison syndrome
9. Merkel cell carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For acromegaly:
A. For initial approval: Laboratory report indicating high pretreatment insulin-like growth factor-1 (IGF-1) level and chart notes indicating an inadequate or partial response to surgery or radiotherapy or a clinical reason for not having surgery or radiotherapy.
B. For continuation: Laboratory report indicating normal current IGF-1 levels or chart notes indicating that the member's IGF-1 level has decreased or normalized since initiation of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Acromegaly
Authorization of 12 months may be granted for the treatment of acromegaly when all of the following criteria are met:
1. Member has a high pretreatment insulin-like growth factor-1 (IGF-1) level for age and/or gender based on the laboratory reference range.

2. Member had an inadequate or partial response to surgery or radiotherapy OR there is a clinical reason why the member has not had surgery or radiotherapy.

B. Carcinoid syndrome
Authorization of 12 months may be granted for treatment of carcinoid syndrome.

C. Vasoactive intestinal peptide tumors (VIPomas)
Authorization of 12 months may be granted for management of symptoms related to hormone hypersecretion of VIPomas.

D. Neuroendocrine tumors (NETs)
1. Authorization of 12 months may be granted for treatment of NETs of the gastrointestinal (GI) tract, lung, and thymus (carcinoid tumors).
2. Authorization of 12 months may be granted for treatment of NETs of the pancreas (islet cell tumors) including gastrinomas, glucagonomas, and insulinomas.
3. Authorization of 12 months may be granted for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

E. Pheochromocytoma and paraganglioma
Authorization of 12 months may be granted for treatment of pheochromocytoma/paraganglioma.

F. Meningiomas
Authorization of 12 months may be granted for treatment of unresectable meningioma.

G. Thymomas and thymic carcinomas
Authorization of 12 months may be granted for treatment of thymoma and thymic carcinoma.

H. Bowel obstruction due to peritoneal carcinomatosis
Authorization of 12 months may be granted for treatment of bowel obstruction due to peritoneal carcinomatosis.

I. Postgastrectomy dumping syndrome
Authorization of 12 months may be granted for treatment of postgastrectomy dumping syndrome.

J. Hepatocellular carcinoma
Authorization of 12 months may be granted for treatment of hepatocellular carcinoma.

K. Zollinger-Ellison syndrome
Authorization of 12 months may be granted for treatment of Zollinger-Ellison syndrome.

L. Merkel cell carcinoma
Authorization of 12 months may be granted as a single agent for treatment of metastatic Merkel cell carcinoma when one of the following criteria is met:
1. The member has contraindication to anti-PD-L1 or anti-PD-1 therapy.
2. The member has disease progression while on anti-PD-L1 or anti-PD-1 therapy.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefits are defined as:
   3. Acromegaly: decreased or normalized IGF-1 level since initiation of therapy.
   4. All other indications: improvement or stabilization in clinical signs and symptoms since initiation of therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Sandostatin LAR.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Thymomas and thymic carcinomas
4. NCCN Guideline: Neuroendocrine and adrenal tumors
5. NCCN Guideline: Central nervous system cancers
6. NCCN Guideline: Merkel cell carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Sandostatin LAR are covered in addition to the following:

A. Neuroendocrine tumors of the gastrointestinal tract, lungs and thymus
B. Neuroendocrine tumors of the pancreas (islet cell tumors)
C. Gastroenteropancreatic neuroendocrine tumors
D. Pheochromocytoma/paraganglioma
E. Meningiomas
F. Thymomas and thymic carcinomas
G. Bowel obstruction due to peritoneal carcinomatosis
H. Postgastrectomy dumping syndrome
I. Hepatocellular carcinoma
J. Zollinger-Ellison syndrome
K. Merkel cell carcinoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Sandostatin LAR to treat neuroendocrine tumors not discussed in the prescribing information can be found in the NCCN Drugs and Biologics Compendium and the Lexi-Drugs database. Use of information in the NCCN Drugs and Biologics Compendium and the Lexi-Drugs database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Sandostatin LAR to treat meningiomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Sandostatin LAR to treat pheochromocytomas and paragangliomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Sandostatin LAR to treat thymomas and thymic carcinomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Sandostatin LAR to treat hepatocellular carcinoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Sandostatin LAR to treat bowel obstruction due to peritoneal carcinomatosis can be found in a randomized, double-blind, non-comparative, pilot study in adults with inoperable symptomatic bowel obstruction due to peritoneal carcinomatosis (n=64), an intention-to-treat analysis showed that IM long-acting repeatable (LAR) octreotide administered with immediate-release (IR) octreotide for the first 6 days of therapy yielded success in 38% (12/32) of patients compared with 28% (9/32) of patients randomized to placebo. In addition to corticosteroids (methylprednisolone 3 to 4 mg/kg/day IV days 1 through 6) and best supportive care, eligible patients were randomized to receive either IM octreotide LAR 30 mg every 28 days and octreotide IR 600 mcg/day (given subQ in 2 to 3 divided doses or by continuous infusion) on days 1 through 6 (n=32), or matching placebo (n=32). The primary endpoint, determined at day 14, was a composite of the absence of a nasogastric tube, vomiting less than twice per day, and no requirement for anticholinergic agents. Because only 64 of the planned 102 patients were enrolled in this study, the primary endpoint could not be attained in the overall population, and the analysis was strictly exploratory. Notably, at baseline, a higher proportion of patients in the octreotide group had a Karnofsky score of less than 50 (46.4%) compared with the placebo group (21.9%). In a subgroup analysis of patients with Karnofsky scores of 50 or greater, a higher response rate was observed in the octreotide group compared with the placebo group (60% (9/15) vs 28% (7/25)). Octreotide was well tolerated, with only 3 drug-related events (severe hyperglycemia, mild injection erythema, and mild local inflammation) attributed to octreotide LAR. However, 28 patients withdrew after randomization (11 in the octreotide group and 17 in the placebo group); insufficient clinical response was the most common reason for discontinuation in the placebo group and death was the most common reason in the octreotide group, most likely due to the poor condition of these patients.

Support for using Sandostatin LAR to treat postgastrectomy dumping syndrome is supported by a prospective study. Didden et al conducted a small, prospective, observational study (n=34) and found both subcutaneous (SUBQ) and long-acting release (LAR) octreotide improved symptoms associated with severe dumping syndrome (early and/or late) after gastric surgery. It should be noted the dropout rate was 59% at the end of a mean of seven and a half years. The mean age was 54 years (range, 27 to 73 years), and the vast majority (71%) of patient underwent partial gastrectomy. Subcutaneous octreotide dose was initiated at 25 to 50 mcg one to three times daily before meals, and intramuscular LAR octreotide was started at 10 mg per month. Dosing regimens were adjusted according to patient response and satisfaction; resulting in a mean SUBQ dose of 183 mcg per day (mcg/d) (range, 50 to 600 mcg), and a mean LAR dose of 475 mcg/d (14 mg per month) (range, 333 to 666 mcg/d). Sixteen (47%) patients discontinued octreotide therapy due to lack of effectiveness (n=7; 21%) or intolerable adverse reactions (n=9; 26%), particularly diarrhea. Among 14 remaining evaluable patients during a mean follow-up of 93 months (range, 7 to 204 months), persistent and frequent early systemic symptom scores were reduced by 50% after initiation of octreotide therapy (p less than 0.05). On the other hand, abdominal symptoms and late dumping symptoms were reduced by 31% and 35%, respectively (all p less than 0.05). The proportion of patients experiencing more than 4 symptoms significantly reduced to 43% during octreotide treatment (p less than 0.05). The 24-hour fecal fat output was 24 grams (normal, less than 7 grams) for patients treated with SUBQ octreotide (n=7) compared with 16 grams for individuals receiving LAR therapy (n=7) (p less than 0.05). Patient ratings on quality of life (80 vs 74) and composite symptom diary score (38 vs 42) were slightly better for SUBQ than LAR formulation.
Additional support for using Sandostatin LAR to treat dumping syndrome can be found in a study by Arts et al. The study included 30 consecutive patients with postoperative dumping, evidenced by oral glucose tolerance test (OGTT) results and insufficient response to dietary measures. OGTT, dumping severity score (summary of scores 0-3 for 8 early and 6 late dumping symptoms), and quality-of-life data were evaluated at baseline, after 3 days of subcutaneous administration of octreotide (0.5 mg), and then after 3 monthly intramuscular injections of octreotide LAR (20 mg). Both formulations of octreotide significantly reduced total dumping severity scores (21.7 +/- 1.6 at baseline, 11.2 +/- 1.2 for subcutaneous and 14.0 +/- 1.8 for LAR formulations; $P < .05$). This reduction was associated with significant improvements in the increase in pulse rate (13.8 +/- 5.8 at baseline vs -0.3 +/- 2.2 and 1.9 +/- 1.7; $P < .05$) as well as the increase in hematocrit level (4.0 +/- 1.4 at baseline vs 0.3 +/- 0.9. and 0.4 +/- 1.0; $P < .05$), and the lowest glycemia level in the OGTT (54.1 +/- 6.7 at baseline vs 98.9 +/- 7.1 and 67.8 +/- 5.9; $P < .05$). LAR octreotide administration significantly improved patients' quality of life. Patients' evaluations of their overall treatment efficacy was higher on LAR compared with the subcutaneous formulation (83% vs 52%; $P = .01$).

Support for using Sandostatin LAR to treat Zollinger-Ellison syndrome can be found in the National Comprehensive Cancer Network's guideline for neuroendocrine and adrenal tumors. The NCCN Guideline supports the use of lanreotide and octreotide long-acting release (LAR) for symptom and tumor control.

Support for using Sandostatin LAR to treat Merkel cell carcinoma can be found in the National Comprehensive Cancer Network's guideline for Merkel cell carcinoma. The NCCN Guideline supports the use of Sandostatin long-acting release (LAR) if anti-PD-L1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 therapy.

VII. REFERENCES

1. Sandostatin LAR Depot [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2023.
2. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado. Updated periodically. https://www.micromedexsolutions.com [available with subscription]. Accessed November 10, 2023.
3. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 14, 2023.
4. The NCCN Clinical Practice Guidelines in Oncology® Neuroendocrine and Adrenal Tumors (Version 1.2023). © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 14, 2023.
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SAPHNELO (anifrolumab-fnia)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Saphnelo is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy.

Limitations of Use: The efficacy of Saphnelo has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Use of Saphnelo is not recommended in these situations.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: Medical records (e.g., chart notes, lab reports) documenting the presence of autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins).
B. Continuation requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Severe active lupus nephritis in a member initiating therapy with Saphnelo.
B. Severe active central nervous system (CNS) lupus (including seizures that are attributed to CNS lupus, psychosis, organic brain syndrome, cerebritis, or CNS vasculitis requiring therapeutic intervention before initiation of anifrolumab) in a member initiating therapy with Saphnelo.
C. Member is using Saphnelo in combination with other biologics.

IV. CRITERIA FOR INITIAL APPROVAL

Systemic lupus erythematosus (SLE)
Authorization of 12 months may be granted for treatment of active SLE when all of the following criteria are met:
A. Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins).
B. The member meets either of the following criteria:
    1. The member is receiving a stable standard treatment for SLE with any of the following (alone or in combination):
        i. Glucocorticoids (e.g., prednisone, methylprednisolone, dexamethasone)
        ii. Antimalarials (e.g., hydroxychloroquine)

iii. Immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate, cyclosporine, cyclophosphamide)

2. The member has a clinical reason to avoid treatment with a standard treatment regimen.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section IV.
C. The member is receiving benefit from therapy. Benefit is defined as disease stability or improvement.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Saphnelo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2023 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus
4. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus
5. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus
6. Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Saphnelo are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The content of the exclusions can be found in the prescribing information.

The British Society for Rheumatology report that ANAs are present in about 95% of SLE patients. If the test for ANAs is negative, there is a low clinical probability of a member having SLE. The presence of anti-dsDNA antibodies, low complement levels or anti-Smith (Sm) antibodies are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE as they are found in other autoimmune rheumatic disorders as well as SLE.

The SLICC group devised evidence-based classification criteria for lupus. These criteria introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items compared with the ACR criteria. These classification criteria may be used to aid diagnosis.

THE EULAR/ACR classification criteria for SLE require ANA antibodies ≥ 1:80 on HEp-2 cells or an equivalent positive test and a classification threshold score of ≥ 10. The classification criteria should not be used as

diagnostic criteria. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended.

VIII. REFERENCES

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SARCLISA (isatuximab-irfc)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Sarclisa is indicated:
1. in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.
2. in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

B. Compendial Use
Multiple Myeloma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Multiple myeloma
Authorization of 12 months may be granted for treatment of multiple myeloma when either of the following criteria is met:
A. The requested medication will be used in combination with pomalidomide and dexamethasone and the member has previously received at least two prior therapies for multiple myeloma, including lenalidomide and a proteasome inhibitor.
B. The requested medication will be used in combination with carfilzomib and dexamethasone and the member has previously received at least one prior line of therapy for multiple myeloma
C. The requested medication will be used in combination with bortezomib, lenalidomide, and dexamethasone as primary therapy for members who are transplant candidates

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
1. No evidence of unacceptable toxicity while on the current regimen AND
2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Sarclisa.
2. The available compendium
a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Multiple Myeloma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Sarclisa to treat multiple myeloma in combination with agents not listed in the prescribing information can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Sarclisa [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; July 2022
2. The NCCN Drugs & Biologics Compendium® ©2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 4, 2023.

SEVENFACT (coagulation factor VIIa [recombinant]-jncw)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Sevenfact [coagulation factor VIIa (recombinant)-jncw] is indicated for the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors.

Limitation of Use:
Sevenfact is not indicated for the treatment of patients with congenital Factor VII deficiency.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Hemophilia A with Inhibitors
Authorization of 12 months may be granted for members 12 years of age or older for treatment of hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

B. Hemophilia B with Inhibitors
Authorization of 12 months may be granted for members 12 years of age or older for treatment of hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Hemophilia A or B with Inhibitors
Authorization for 12 months may be granted for members 12 years of age or older when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat Hemophilia A or B with inhibitors
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. APPENDIX: Inhibitors - Bethesda Units (BU)

The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Sevenfact.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. WFH Guidelines for the Management of Hemophilia, 3rd edition.
4. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Sevenfact are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Sevenfact [package insert]. Puteaux , France: Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.); November 2022.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
3. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 8, 2023.

SIGNIFOR LAR (pasireotide)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option
   2. Treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative

B. Compendial Uses[2]
   1. Carcinoid syndrome
   2. Metastatic neuroendocrine tumors (NETs) of the gastrointestinal (GI) tract (carcinoid tumors)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Acromegaly:
   1. For initial approval: Laboratory report indicating high pretreatment insulin-like growth factor-1 (IGF-1) level and chart notes indicating an inadequate or partial response to surgery or a clinical reason for not having surgery.
   2. For continuation: Laboratory report indicating normal current IGF-1 levels or chart notes indicating that the member's IGF-1 level has decreased or normalized since initiation of therapy.

B. Cushing's disease:
   1. For initial requests, pretreatment cortisol level as measured by one of the following tests:
      a. Urinary free cortisol (UFC)
      b. Late-night salivary cortisol
      c. 1 mg overnight dexamethasone suppression test (DST)
      d. Longer, low dose DST (2 mg per day for 48 hours)
   2. For continuation of therapy (if applicable), laboratory report indicating current cortisol level has decreased from baseline as measured by one of the following tests:
      a. Urinary free cortisol (UFC)
      b. Late-night salivary cortisol
      c. 1 mg overnight dexamethasone suppression test (DST)
      d. Longer, low dose DST (2 mg per day for 48 hours)

III. CRITERIA FOR INITIAL APPROVAL

A. Acromegaly

Authorization of 12 months may be granted for treatment of acromegaly when all of the following criteria are met:

1. Member has a high pretreatment insulin-like growth factor-1 (IGF-1) level for age and/or gender based on the laboratory reference range.
2. Member has had an inadequate or partial response to surgery OR there is a clinical reason why the member has not had surgery.

B. Cushing's disease
Authorization of 12 months may be granted for treatment of Cushing's disease when the member has had surgery that was not curative OR the member is not a candidate for surgery.

C. Neuroendocrine tumors (NETs) of the gastrointestinal (GI) tract (carcinoid tumors)
Authorization of 12 months may be granted for treatment of metastatic NETs of the GI tract (carcinoid tumors).

D. Carcinoid syndrome
Authorization of 12 months may be granted for treatment of carcinoid syndrome.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. Acromegaly: decreased or normalized IGF-1 level since initiation of therapy.
    2. Cushing's disease (any of the following):
        a. Lower cortisol levels since the start of therapy per one of the following tests:
            i. Urinary free cortisol (UFC)
            ii. Late-night salivary cortisol
            iii. 1 mg overnight dexamethasone suppression test (DST)
            iv. Longer, low dose DST (2 mg per day for 48 hours)
        b. Improvement in signs and symptoms of the disease
    3. All other indications: improvement or stabilization of clinical signs and symptoms since initiation of therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Signifor LAR.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Acromegaly: an endocrine society clinical practice guideline.
4. American Association of Clinical Endocrinologists Acromegaly Guidelines Task Force. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly – 2011 update.
5. Treatment of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Signifor LAR are covered in addition to the following:
1. Carcinoid syndrome
2. Metastatic neuroendocrine tumors (NETs) of the gastrointestinal (GI) tract (carcinoid tumors)

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Signifor LAR to treat carcinoid syndrome and metastatic neuroendocrine tumors (NETs) of the gastrointestinal tract can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for utilizing a high pretreatment insulin-like growth factor-1 (IGF-1) as a diagnostic requirement and targeting IGF-1 in patients with acromegaly is supported by two professional guidelines.
According to Katznelson et al, the biochemical target goal is an age-normalized IGF-1. An age-normalized IGF-1 signifies control of acromegaly.
According to the Endocrine Society, IGF-1 should be measured and patients with elevated or equivocal serum IGF-1 levels should have the diagnosis confirmed by finding lack of suppression of growth hormone to less than 1 microgram/L following documented hyperglycemia during an oral glucose load. The Endocrine Society also supports the normalization of IGF-1 as the biochemical target goal of therapy with Signifor LAR.

VII. REFERENCES

1. Signifor LAR [package insert]. Lebanon, NJ: Recordati Rare Diseases Inc; June 2020.
2. IBM Micromedex® DRUGDEX® (electronic version). Micromedex Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com [available with subscription]. Accessed November 10, 2023.
3. Katznelson L, Laws ER, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99:3933-3951.
4. American Association of Clinical Endocrinologists Acromegaly Guidelines Task Force. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly – 2011 update. *Endocr Pract*. 2011;17(suppl 4):1-44.
5. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2015;100(8):2807-31.
6. Gadelha MR, Bronstein MD, Brue T, et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomized, phase 3 trial. *Lancet Diabetes Endocrinol*. 2014;2:875-84.
7. Colao A, Bronstein MD, Freda P, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *J Clin Endocrinol Metab.* 2014;99:791–799.

SIMPONI ARIA (golimumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate
   2. Treatment of active psoriatic arthritis (PsA) in patients 2 years of age and older
   3. Treatment of adult patients with active ankylosing spondylitis (AS)
   4. Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older

B. Compendial Uses
   1. Non-radiographic axial spondyloarthritis
   2. Oligoarticular juvenile idiopathic arthritis
   3. Immune checkpoint inhibitor-related toxicities – inflammatory arthritis

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Rheumatoid arthritis (RA)
   1. For initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.
   2. For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

B. Psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), and articular juvenile idiopathic arthritis (JIA)
   For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

C. Immune checkpoint inhibitor-related toxicity
   For initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Rheumatoid arthritis (RA)
Authorization of 12 months may be granted for treatment of moderately to severely active rheumatoid arthritis when either of the following criteria is met:
   1. Simponi Aria will be used in combination with methotrexate.
   2. The member has a clinical reason to avoid methotrexate (e.g., breastfeeding, pregnancy or currently planning pregnancy, renal or hepatic impairment, previous intolerance to methotrexate).

B. Psoriatic arthritis (PsA)
Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

C. Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)
Authorization of 12 months may be granted tor treatment of active ankylosing spondylitis or active non-radiographic axial spondyloarthritis.

D. Articular juvenile idiopathic arthritis (JIA)
Authorization of 12 months may be granted for treatment of active articular juvenile idiopathic arthritis.

E. Immune checkpoint inhibitor-related toxicity
Authorization of 12 months may be granted for treatment of refractory or severe immunotherapy-related inflammatory arthritis that has not responded to systemic corticosteroids.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Immune checkpoint inhibitor-related toxicity
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. All other indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Simponi Aria.
2. Simponi Aria is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Simponi Aria.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
3. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update
4. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis
5. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis
6. EULAR recommendations for management of psoriatic arthritis with pharmacological therapies: 2019 update
7. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and Non radiographic axial spondyloarthritis
8. 2016 update of the international ASAS-EULAR management recommendations for axial spondyloarthritis
9. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis
10. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis
11. NCCN guideline: Management of immunotherapy-related toxicities

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Simponi Aria are covered in addition to the following:
A. Non-radiographic axial spondyloarthritis
B. Oligoarticular juvenile idiopathic arthritis

C. Immune checkpoint inhibitor-related toxicity – inflammatory arthritis

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

According to the 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis, in patients who are DMARD-naïve (disease-modifying antirheumatic drug) methotrexate is strongly recommended over hydroxychloroquine or sulfasalazine in patients with moderate-to-high disease activity. Methotrexate is conditionally recommended over leflunomide.

Non-radiographic axial spondyloarthritis is listed as an approvable indication along with ankylosing spondylitis. The 2016 update of the ASAS-EULAR recommendations for the treatment of non-radiographic axial spondyloarthritis support golimumab along with other TNF inhibitors. Support for including non-radiographic axial spondyloarthritis can be found in the 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network guidelines. In adults with active ankylosing spondylitis or active non-radiographic axial spondyloarthritis despite treatment with NSAIDs, tumor necrosis factor inhibitors (TNFs) are strongly recommended over no treatment with TNFs.

Support for using Simponi Aria for oligoarticular juvenile idiopathic arthritis can be found in the 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. For patients who have had an inadequate response or intolerance to non-biologic DMARDs, the next step is a biologic DMARD such as golimumab. The guideline indicates there is no preferred agent.

Support for using Simponi Aria to manage immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for the management of immunotherapy-related toxicities supports the use of adding Simponi Aria for moderate or severe inflammatory arthritis as additional disease modifying antirheumatic drug (DMARD) therapy if no improvement after holding immunotherapy and treating with oral corticosteroids or if unable to taper corticosteroids, or no response to conventional synthetic DMARDs.

VII. REFERENCES

1. Simponi Aria [package insert]. Horsham, PA: Janssen Biotech, Inc.; February 2021.
2. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685-699. doi:10.1136/annrheumdis-2019-216655.
3. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthrit Care Res*. 2021;0:1-16.
4. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheum*. 2018;71:5-32.
5. Gossec L, Baraliakos X, Kerschbaumer A. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis*. 2020;79(6):700-712.
6. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol.* 2019;71(10):1599-1613. doi:10.1002/art.41042.
7. van der Heijde D, Ramiro S, Landewe R, et al. 2016 Update of the international ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis.* 2017;76(6):978-991.
8. Ringold S, Angeles-Han S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. *American College of Rheumatology.* 2019;1-18.
9. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2022;74(4):553-569.
10. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed June 9, 2023.

SKYRIZI (risankizumab-rzaa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. Treatment of moderate-to-severe plaque psoriasis (PsO) in adults who are candidates for systemic therapy or phototherapy
B. Treatment of active psoriatic arthritis (PsA) in adults
C. Treatment of moderately to severely active Crohn's disease (CD) in adults

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Plaque psoriasis (PsO)
   1. Initial requests:
      i. Chart notes or medical record documentation of affected area(s) and body surface area (BSA) affected (if applicable).
      ii. Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.
   2. Continuation requests: Chart notes or medical record documentation of decreased body surface area (BSA) affected and/or improvement in signs and symptoms.

B. Psoriatic arthritis (PsA)
   1. Initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.
   2. Continuation requests: Chart notes or medical record documentation supporting positive clinical response.

C. Crohn's disease (CD)
   Continuation requests: Chart notes or medical record documentation supporting positive clinical response to therapy or remission.

III. CRITERIA FOR INITIAL APPROVAL

A. Plaque psoriasis (PsO)

1. Authorization of 12 months may be granted for adult members who have previously received a biologic or targeted synthetic drug (e.g., Sotyktu, Otezla) indicated for the treatment of moderate to severe plaque psoriasis.

2. Authorization of 12 months may be granted for adult members for treatment of moderate to severe plaque psoriasis when any of the following criteria is met:
   i. Crucial body areas (e.g., hands, feet, face, neck, scalp, genitals/groin, intertriginous areas) are affected.

ii. At least 10% of body surface area (BSA) is affected.
iii. At least 3% of body surface area (BSA) is affected and the member meets either of the following criteria:
    a. Member has had an inadequate response or intolerance to either phototherapy (e.g., UVB, PUVA) or pharmacologic treatment with methotrexate, cyclosporine, or acitretin.
    b. Member has a clinical reason to avoid pharmacologic treatment with methotrexate, cyclosporine, and acitretin (see Appendix).

B. Psoriatic arthritis (PsA)

1. Authorization of 12 months may be granted for adult members who have previously received a biologic or targeted synthetic drug (e.g., Rinvoq, Otezla) indicated for active psoriatic arthritis.

2. Authorization of 12 months may be granted for adult members for treatment of active psoriatic arthritis when either of the following criteria is met:
    i. Member has mild to moderate disease and meets one of the following criteria:
        a. Member has had an inadequate response to methotrexate, leflunomide, or another conventional synthetic drug (e.g., sulfasalazine) administered at an adequate dose and duration.
        b. Member has an intolerance or contraindication to methotrexate or leflunomide (see Appendix), or another conventional synthetic drug (e.g., sulfasalazine).
        c. Member has enthesitis or predominantly axial disease.
    ii. Member has severe disease.

C. Crohn's disease (CD)

Authorization of 12 months may be granted for adult members for the treatment of moderately to severely active Crohn's disease.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Plaque psoriasis (PsO)

Authorization of 12 months may be granted for all adult members (including new members) who are using the requested medication for moderate to severe plaque psoriasis and who achieve or maintain a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when either of the following is met:

1. Reduction in body surface area (BSA) affected from baseline
2. Improvement in signs and symptoms from baseline (e.g., itching, redness, flaking, scaling, burning, cracking, pain)

B. Psoriatic arthritis (PsA)

Authorization of 12 months may be granted for all adult members (including new members) who are using the requested medication for psoriatic arthritis and who achieve or maintain a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:

1. Number of swollen joints
2. Number of tender joints
3. Dactylitis
4. Enthesitis
5. Axial disease
6. Skin and/or nail involvement

C. Crohn's Disease (CD)

1. Authorization of 12 months may be granted for all adult members (including new members) who are using the requested medication for moderately to severely active Crohn's disease and who achieve or maintain remission.

2. Authorization of 12 months may be granted for all adult members (including new members) who are using the requested medication for moderately to severely active Crohn's disease and who achieve or maintain a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:
    i. Abdominal pain or tenderness
    ii. Diarrhea
    iii. Body weight
    iv. Abdominal mass
    v. Hematocrit
    vi. Appearance of the mucosa on endoscopy, computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound
    vii. Improvement on a disease activity scoring tool (e.g., Crohn's Disease Activity Index [CDAI] score)

V. APPENDIX

Examples of Clinical Reasons to Avoid Pharmacologic Treatment with Methotrexate, Cyclosporine, Acitretin, or Leflunomide

1. Clinical diagnosis of alcohol use disorder, alcoholic liver disease or other chronic liver disease
2. Drug interaction
3. Risk of treatment-related toxicity
4. Pregnancy or currently planning pregnancy
5. Breastfeeding
6. Significant comorbidity prohibits use of systemic agents (e.g., liver or kidney disease, blood dyscrasias, uncontrolled hypertension)
7. Hypersensitivity
8. History of intolerance or adverse event

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Skyrizi.
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology
3. AAD Guidelines of care for the management of psoriasis and psoriatic arthritis.
4. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics
5. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis
6. ACG Clinical Guideline: Management of Crohn's Disease in Adults

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Skyrizi are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCES

1. Skyrizi [package insert]. North Chicago, IL: AbbVie Inc.; May 2023.
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10. Lichtenstein GR, Loftus Jr EV, Isaacs KI, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113:481-517.
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SKYSONA (elivaldogene autotemcel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Skysona is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active cerebral adrenoleukodystrophy refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5-9.

This indication is approved under accelerated approval based on 24-month Major Functional Disability (MFD)-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use:

- Skysona does not treat or prevent adrenal insufficiency.
- An immune response to Skysona may cause rapid loss of efficacy of Skysona in patients with full deletions of the human adenosine triphosphate binding cassette, sub family D, member 1 (*ABCD1*) gene.
- Skysona has not been studied in CALD secondary to head trauma.
- Given the risk of hematologic malignancy with Skysona, and unclear long-term durability of Skysona and human adrenoleukodystrophy protein (ALDP) expression, careful consideration should be given to the timing of treatment for each boy and treatment of boys with isolated pyramidal tract disease as clinical manifestations do not usually occur until adulthood.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Chart notes, medical records, or lab results documenting all of the following:

A. Variant in the *ABCD1* gene
B. Elevated very long chain fatty acids (VLCFA) values
C. Active central nervous system (CNS) disease on central radiographic review of brain magnetic resonance imaging (MRI) demonstrating:
    1. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, and
    2. Gadolinium enhancement on MRI of demyelinating lesions
D. Neurologic Function Score (NFS) less than or equal to 1

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:

A. Skysona will be used to treat or prevent adrenal insufficiency.
B. Member has either of the following:
    1. Full deletions of the *ABCD1* transgene.
    2. CALD secondary to head trauma.

IV. CRITERIA FOR INITIAL APPROVAL

Cerebral Adrenoleukodystrophy (CALD)
Authorization of 3 months for a one-time administration may be granted for treatment of cerebral adrenoleukodystrophy (CALD) when all of the following criteria are met:

A. Member must be a male between the ages of 4 and 17 years of age
B. Member has a diagnosis of adrenoleukodystrophy confirmed by both of the following:
    1. The presence of a pathogenic (or likely pathogenic) variant in the *ABCD1* gene as detected by genetic testing, and
    2. Elevated very long chain fatty acids (VLCFA) values per reference range of the laboratory performing the test
C. Member has early active disease as defined by all of the following:
    1. Central radiographic review of brain MRI demonstrating both of the following:
        a. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, and
        b. Gadolinium enhancement on MRI of demyelinating lesions
    2. NFS of less than or equal to 1
D. Member has not received Skysona or any other gene therapy previously
E. Member has not received a prior allogeneic hematopoietic stem cell transplant (allo-HSCT)

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Skysona.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. X-Linked Adrenoleukodystrophy - Gene Reviews

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Skysona are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Skysona [package insert]. Somerville, MA: Bluebird bio, Inc.; September 2022.
2. Raymond GV, Moser AB, Fatemi A. X-Linked Adrenoleukodystrophy. 1999 Mar 26 [Updated 2023 Apr 6]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1315/. Accessed November 7, 2023.

SOLIRIS (eculizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. Paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
B. Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy
C. Generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive
D. Neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) positive.

Limitation of Use
Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. For initial requests:
   1. Paroxysmal nocturnal hemoglobinuria (PNH): flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency
   2. Generalized myasthenia gravis (gMG): Anti-acetylcholine receptor (AchR) antibody positive and use of two immunosuppressive therapies
   3. Neuromyelitis optica spectrum disorder (NMOSD): Immunoassay used to confirm anti-aquaporin-4 (AQP4) antibody is present
B. For continuation requests for PNH, aHUS, NMOSD: Chart notes or medical record documentation supporting benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Paroxysmal Nocturnal Hemoglobinuria (PNH)
Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:
1. The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) as demonstrated by either of the following:
   i. At least 5% PNH cells
   ii. At least 51% of GPI-AP deficient poly-morphonuclear cells
2. Flow cytometry is used to demonstrate GPI-APs deficiency

B. Atypical Hemolytic Uremic Syndrome (aHUS)
Authorization of 6 months may be granted for treatment of atypical hemolytic uremic syndrome (aHUS) that is not caused by Shiga toxin.

C. Generalized Myasthenia Gravis (gMG)

Authorization of 12 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:

1. The member is anti-acetylcholine receptor (AchR) antibody positive.
2. The member has had an inadequate response to at least two immunosuppressive therapies listed below:
   i. azathioprine
   ii. cyclosporine
   iii. mycophenolate mofetil
   iv. tacrolimus
   v. methotrexate
   vi. cyclophosphamide
   vii. rituximab

D. Neuromyelitis Optica Spectrum Disorder (NMOSD)

Authorization of 12 months may be granted for treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:

1. The member is anti-aquaporin-4 (AQP4) antibody positive.
2. The member exhibits one of the following core clinical characteristics of NMOSD:
   i. Optic neuritis
   ii. Acute myelitis
   iii. Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
   iv. Acute brainstem syndrome
   v. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
   vi. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Paroxysmal Nocturnal Hemoglobinuria (PNH)

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Soliris.
2. The member is receiving benefit from therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels).

B. Atypical Hemolytic Uremic Syndrome (aHUS)

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Soliris.
2. The member is receiving benefit from therapy (e.g., normalization of lactate dehydrogenase [LDH] levels, platelet counts).

C. Neuromyelitis Optica Spectrum Disorder (NMOSD)

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Soliris.
2. The member is receiving benefit from therapy (e.g., reduction in number of relapses as compared to baseline).

D. Generalized Myasthenia Gravis (gMG)

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Soliris.
2. The member is receiving benefit from therapy

V. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Soliris.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy.
4. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry.
5. International consensus guidance for management of myasthenia gravis
6. An international consensus approach to the management of atypical hemolytic uremic syndrome in children.
7. International consensus guidance for management of myasthenia gravis: 2020 update
8. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Soliris are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using percentage of PNH cells or percentage of GPI-AP deficiency poly-morphonuclear cells can be found in the guidelines for diagnosis of PNH (Borowitz et al and Preis et al). Flow cytometry is the gold standard for assessing the percentage of GPI-AP deficient poly-morphonuclear cells. Classic PNH is defined as greater than 50% of GPI-AP deficient PMNs. It is also possible to diagnose PNH by assessing the percentage of PNH cells. Most clinical trials for the complement inhibitors required at least 10% PNH cells, but the trials associated with Ultomiris only required 5% PNH cells. Therefore, the baseline requirement for all complement inhibitor programs will be at least 5%.

Support for the list of prerequisite therapies in generalized myasthenia gravis can be found in the guidelines for the management of MG (Narayanaswami et al). The guidelines support the use of azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide and rituximab as immunosuppressive therapies for gMG.

Support for the list of core clinical characteristics of NMOSD can be found in the International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (Wingerchuk et al). There are six clinical characteristics cited in the diagnostic criteria:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical
- diencephalic MRI lesions (figure 3)
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

VIII. REFERENCES

1. Soliris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; November 2020.

2. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. *Hematology.* 2011; 21-29.
3. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol*. Published online: January 1, 2016.
4. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology*. 2021;96(3):114-122.
5. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85:177-189.
6. Borowitz MJ, Craig F, DiGiuseppe JA, et al. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry. *Cytometry B Clin Cytom*. 2010: 78: 211-230.
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8. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.
9. Dezern AE, Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018 Jan;94(1):16-22.

SPEVIGO (spesolimab-sbzo)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication[1]
For the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients 12 years of age and older and weighing at least 40 kg.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Generalized pustular psoriasis (GPP) flare
Chart notes or medical record documentation of affected area(s) must be available, upon request, for all submissions.

B. Generalized pustular psoriasis (GPP) when not experiencing a flare
For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Generalized pustular psoriasis (GPP) flare
Authorization of 1 month may be granted for treatment of generalized pustular psoriasis flares in members 12 years of age or older when all of the following criteria are met:
1. Member has a known documented history of GPP (either relapsing [greater than 1 episode] or persistent [greater than 3 months]).
2. Member is presenting with primary, sterile, macroscopically visible pustules (new or worsening) on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques).
3. At least 5% body surface area (BSA) is covered with erythema and the presence of pustules.

B. Generalized pustular psoriasis (GPP) when not experiencing a flare
Authorization of 12 months may be granted for treatment of generalized pustular psoriasis in members 12 years of age or older when all of the following criteria are met:
1. Member has a known documented history of GPP (either relapsing [greater than 1 episode] or persistent [greater than 3 months]).
2. Member meets either of the following:
    i. Member has had a history of at least two moderate-to-severe GPP flares (e.g., at least 5% body surface area is covered with erythema and the presence of pustules; Generalized Pustular Psoriasis Physician Global Assessment [GPPPGA] total score of greater or equal to 3).
    ii. Member has a history of flaring while on concomitant treatment (e.g., retinoids, methotrexate, cyclosporine).
3. Member currently has clear to almost clear skin.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Generalized pustular psoriasis (GPP) flare
All members 12 years of age or older requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. Generalized pustular psoriasis (GPP) when not experiencing a flare
Authorization of 12 months may be granted for members 12 years of age or older when both of the following criteria are met:
1. The member is currently receiving therapy with Spevigo.
2. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Spevigo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Spevigo [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2024.
2. Bachelez H, Choon SE, Marrakchi S, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. *N Engl J Med*. 2021;385(26):2431-2440.
3. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(11):1792-1799.
4. Morita A, Choon SE, Bachelez H, et al. Design of Effisayil™ 2: A Randomized, Double-Blind, Placebo-Controlled Study of Spesolimab in Preventing Flares in Patients with Generalized Pustular Psoriasis. *Dermatol Ther (Heidelb)*. 2023;13(1):347-359.
5. Armstrong AW, Elston CA, Elewski BE, et al. Generalized pustular psoriasis: A consensus statement from the National Psoriasis Foundation. *J Am Acad Dermatol*. 2024 Apr;90(4):727-730.

SPINRAZA (nusinersen)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Spinraza is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all initial submissions: Deletion or mutation at the SMN1 allele confirmed by genetic testing.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy.

IV. CRITERIA FOR INITIAL APPROVAL

Spinal muscular atrophy (SMA)
Authorization of 12 months may be granted for treatment of SMA when all of the following criteria are met:
A. Member has a diagnosis of SMA confirmed by genetic testing showing deletion or mutation at the SMN1 allele.
B. Member has Type 1, Type 2 or Type 3 SMA.
C. Member will not use Spinraza and Evrysdi concomitantly.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Spinraza.
B. Spinraza is being used to treat an indication enumerated in Section IV.
C. The member is receiving benefit from therapy.
D. Member will not use Spinraza and Evrysdi concomitantly.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Spinraza.
2. The available compendium

a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. Spinal muscular atrophy: diagnosis and management in a new therapeutic era.
4. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders.
5. Consensus statement for standard care in spinal muscular atrophy.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Spinraza are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using genetic testing as a requirement for diagnosis is supported by a guideline by Arnold and colleagues. Molecular genetic testing is the standard tool for the diagnosis of SMA. Patients with SMA have homozygous loss of function of both *SMN1* copies. Genetic testing for homozygous deletion will confirm the disease in 95% of patients irrespective of disease severity. All other patients with SMN-related SMA will be compound heterozygotes with a single *SMN1* deletion and a frameshift, nonsense, or missense mutation in the other *SMN1* copy. If homozygous *SMN1* deletion is not evident in a patient with suspected SMA, *SMN1* dosage analysis and sequencing of the remaining *SMN1* gene should be performed.
The traditional classification strategy divides patients into four groups. Type 1 is the most common and severe form. Patients experience an onset in the first six months of life and are never able to sit upright. Patients with Type 2 SMA are usually diagnosed in the first eighteen months of life. The ability to sit is typically achieved by 9 months and patients will never stand or walk independently, but some patients will be able to stand with assistance of bracing or a standing frame. Patients with Type 3 SMA typically exhibit symptoms after 18 months. The patient is able to stand or walk without support, but many patients lose these abilities when the disease progresses. Patients with type 4 SMA experience symptoms starting in adulthood and are ambulatory. The studies cited in the prescribing information included patients with type 1, 2 and 3 SMA.

VIII. REFERENCES

1. Spinraza [package insert]. Cambridge, MA: Biogen Inc.; February 2023.
2. Arnold WD, Kassar D, Kissel JT, et al. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle & Nerve*. 2015;51(2):157-167.
3. Burgunder JM, Schols L, Baets J, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. *European J Neurol*. 2011;18:207-217.
4. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388:3017-26.
5. Ionis Pharmaceuticals, Inc. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Infants with Spinal Muscular Atrophy. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). 2000- [2016 Feb 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT02193074.
6. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018; 378:625-635.
7. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard care in spinal muscular atrophy. *J Child Neurol*. 2007;22(8):1027-1049.

STELARA (ustekinumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. For the treatment of patients 6 years or older with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy.
   2. For the treatment of patients 6 years or older with active psoriatic arthritis (PsA).
   3. For the treatment of adult patients with moderately to severely active Crohn's disease (CD).
   4. For the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

B. Compendial Uses
   Immune checkpoint inhibitor-related toxicity

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Ulcerative colitis (UC) and Crohn's disease (CD)
   For continuation requests: Chart notes or medical record documentation supporting positive clinical response to therapy or remission.

B. Immune checkpoint inhibitor-related toxicity (initial requests only)
   Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

C. All other indications
   For continuation requests: Chart notes or medical record documentation supporting positive clinical response to therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Plaque psoriasis (PsO)
Authorization of 12 months may be granted for treatment of moderate to severe plaque psoriasis.

B. Psoriatic arthritis (PsA)
Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

C. Crohn's disease (CD)
Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

D. Ulcerative colitis (UC)
Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

E. Immune checkpoint inhibitor-related toxicity

Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related diarrhea or colitis when the member has had an inadequate response, intolerance, or contraindication to infliximab or vedolizumab.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Crohn's disease (CD)

Authorization for 12 months may be granted for moderately to severely active Crohn's disease when both of the following criteria are met:

1. The member is currently receiving therapy with Stelara.
2. The member is receiving benefit from therapy. Benefit is defined as one of the following:
    i. Member has achieved or maintained remission.
    ii. Member has achieved or maintained a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:
        a. Abdominal pain or tenderness
        b. Diarrhea
        c. Body weight
        d. Abdominal mass
        e. Hematocrit
        f. Appearance of the mucosa on endoscopy, computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound
        g. Improvement on a disease activity scoring tool (e.g., Crohn's Disease Activity Index [CDAI] score)

B. Ulcerative colitis (UC)

Authorization for 12 months may be granted for moderately to severely active ulcerative colitis when both of the following criteria are met:

1. The member is currently receiving therapy with Stelara.
2. The member is receiving benefit from therapy. Benefit is defined as one of the following:
    i. Member has achieved or maintained remission.
    ii. Member has achieved or maintained a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:
        a. Stool frequency
        b. Rectal bleeding
        c. Urgency of defecation
        d. C-reactive protein (CRP)
        e. Fecal calprotectin (FC)
        f. Appearance of the mucosa on endoscopy, computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound
        g. Improvement on a disease activity scoring tool (e.g., Ulcerative Colitis Endoscopic Index of Severity [UCEIS], Mayo score)

C. Immune checkpoint inhibitor-related toxicity

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

D. All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Stelara.
2. Stelara is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Stelara.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Management of immunotherapy-related toxicities
4. An evidence-based systematic review on medical therapies for inflammatory bowel disease.
5. ACG Clinical Guideline: Management of Crohn's Disease in Adults
6. 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults
7. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis
8. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Stelara are covered in addition to immune checkpoint inhibitor-related toxicity.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Stelara to manage immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for the management of immunotherapy-related toxicities supports the use of adding Stelara for mild (G1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin. Additionally, consider Stelara for infliximab- and/or vedolizumab-refractory moderate (G2) or severe (G3-4) diarrhea or colitis.

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SUBCUTANOUS IMMUNE GLOBULINS

CUTAQUIG (immune globulin subcutaneous [Human] - hipp, 16.5%)
CUVITRU (immune globulin subcutaneous [Human] 20%)
HIZENTRA (immune globulin subcutaneous [Human] 20%)
HYQVIA (immune globulin subcutaneous [Human] 10%)
XEMBIFY (immune globulin subcutaneous [Human] – klhw, 20%)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Cutaquig (Immune Globulin Subcutaneous [Human] - hipp, 16.5% Solution)
   Cutaquig is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older.
2. Cuvitru (Immune Globulin Subcutaneous [Human], 20% Solution)
   Cuvitru is indicated as replacement therapy for primary humoral immunodeficiency in adult and pediatric patients two years of age and older.
3. Hizentra (Immune Globulin Subcutaneous [Human], 20% Liquid)
   a. Hizentra is indicated as replacement therapy for primary humoral immunodeficiency in adults and pediatric patients 2 years of age and older.
   b. Hizentra is indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.
      Limitations of Use:
      Hizentra maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Maintenance therapy beyond these periods should be individualized based upon the patient's response and need for continued therapy.
4. HyQvia (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase)
   a. HyQvia is indicated for the treatment of primary immunodeficiency in adults and pediatric patients two years of age and older.
   b. HyQvia is indicated for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment in adults.
5. Xembify (Immune Globulin Subcutaneous [Human} – klhw, 20% Solution)
   Xembify is indicated for treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older.

B. Compendial Uses
1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy
2. Acquired thrombocytopenia
3. Antiphospholipid syndrome
4. Asthma
5. Autoimmune hemolytic anemia
6. Autoimmune neutropenia
7. Bone marrow transplant/hematopoietic stem cell transplant
8. Cerebellar ataxia due to Epstein-Barr virus infection
9. Clostridium difficile colitis
10. Adjunct to Crohn's disease treatment
11. Cytomegalovirus treatment and prophylaxis
12. Desensitization therapy – heart transplant
13. Dermatomyositis

14. Diabetic amyotrophy
15. Hopkins' syndrome
16. Acute disseminated encephalomyelitis
17. Prophylaxis of enteritis due to rotavirus
18. Epilepsy
19. Gastroenteritis
20. Granulomatosis with polyangiitis
21. Guillain-Barre syndrome
22. Hemolytic disease of fetus or newborn due to RhD isoimmunization, prophylaxis
23. Hemophagocytic syndrome
24. Induction of Factor VIII immune tolerance
25. Measles (Rubeola) prophylaxis
26. Moderate and severe immune checkpoint inhibitor-related toxicities
27. Hypogammaglobulinemia from CAR-T therapy
28. Herpes gestationis
29. Prevention of bacterial infections in HIV infected patients
30. Prevention of bacterial infections in post-surgical or ICU patients
31. Isaacs syndrome
32. Japanese encephalitis virus disease
33. Severe IgA nephropathy
34. Lambert-Eaton myasthenic syndrome
35. Linear IgA dermatosis
36. Lysinuric protein intolerance
37. Prevention of bacterial infections in patients with multiple myeloma
38. Multiple sclerosis
39. Myasthenia gravis
40. Myocarditis
41. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
42. Neonatal jaundice
43. Otitis media
44. Paraneoplastic visual loss
45. Polyarteritis nodosa
46. Polymyositis
47. Post-transplant lymphoproliferative disorder
48. Pure red cell aplasia
49. Pyoderma gangrenosum
50. Renal transplant rejection
51. Respiratory syncytial virus infection
52. Sepsis
53. Stevens-Johnson syndrome
54. Stiff-person syndrome
55. Systemic lupus erythematosus
56. Systemic onset juvenile chronic arthritis
57. Systemic vasculitis
58. Tetanus treatment and prophylaxis
59. Fetal or neonatal thrombocytopenia
60. Toxic epidermal necrolysis
61. Toxic necrotizing fasciitis
62. Toxic shock syndrome
63. Heart transplant rejection
64. Desensitization of highly sensitized patients awaiting renal transplantation
65. Uveitis
66. Varicella prophylaxis
67. Von Willebrand disorder
68. Idiopathic thrombocytopenic purpura (ITP)
69. Multifocal motor neuropathy
70. Kawasaki syndrome
71. B-cell chronic lymphocytic leukemia (CLL)

C. Nationally Covered Indication
Centers for Medicare and Medicaid Services guidelines provide coverage for IG for the following autoimmune mucocutaneous conditions pursuant to the criteria in Section III:
1. Pemphigus vulgaris
2. Pemphigus foliaceus
3. Bullous pemphigoid
4. Mucous membrane pemphigoid (cicatricial pemphigoid)
5. Epidermolysis bullosa acquisita

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submission (where applicable):
A. Myasthenia gravis
1. Clinical records describing standard treatments tried and failed
B. Secondary hypogammaglobulinemia (CLL, , BMT/HSCT recipients)
1. Copy of laboratory report with pre-treatment serum IgG level
C. Multifocal motor neuropathy (MMN)
1. Pre-treatment electrodiagnostic studies (electromyography [EMG] or nerve conduction studies [NCS])
D. Dermatomyositis and polymyositis
1. Clinical records describing standard treatments tried and failed
E. Lambert-Eaton Myasthenic Syndrome (LEMS)
1. Neurophysiology studies (e.g., electromyography)
2. A positive anti- P/Q type voltage-gated calcium channel antibody test
F. Idiopathic thrombocytopenic purpura
1. Laboratory report with pre-treatment/current platelet count
2. Chronic/persistent ITP: copy of medical records supporting trial and failure with corticosteroid or anti-D therapy (unless contraindicated)
G. Stiff-person syndrome
1. Anti-glutamic acid decarboxylase (GAD) antibody testing results
2. Clinical records describing standard treatments tried and failed
H. Toxic shock syndrome or toxic necrotizing fasciitis due to group A streptococcus
1. Documented presence of fasciitis (toxic necrotizing fasciitis due to group A streptococcus only)
2. Microbiological data (culture or Gram stain)

III. CRITERIA FOR INITIAL APPROVAL- HOME ADMINISTRATION

Primary Immune Deficiency Disorder, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
Authorization of 6 months may be granted for treatment of primary immune deficiency disorder when the following criteria are met:
A. The requested subcutaneous immune globulin preparation will be administered in the home.
B. The treating practitioner has determined that administration of the SCIG in the member's home is medically necessary and appropriate.
C. The member has a primary immune deficiency disorder and has one of the following ICD-10 codes as their diagnosis: D80.0 (hereditary hypogammaglobulinemia), D80.2 (selective deficiency of immunoglobulin A), D80.3 (selective deficiency of immunoglobulin G subclasses), D80.4 (selective deficiency of immunoglobulin M), D80.5 (immunodeficiency with increased immunoglobulin M), D80.6 (antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia), D80.7 (transient hypogammaglobulinemia of infancy), D81.0 (severe combined immunodeficiency [SCID] with reticular dysgenesis), D81.1 (SCID with low T- and B-cell numbers), D81.2 (SCID with low or normal B-cell numbers), D81.5 (purine nucleoside phosphorylase deficiency), D81.6 (major histocompatibility complex class I deficiency), D81.7 (major histocompatibility complex class II deficiency), D81.82 (activated phosphoinositide 3-kinase delta syndrome), D81.89 (other combined immunodeficiencies), D81.9 (combined immunodeficiency, unspecified), D82.0 (Wiskott-Aldrich syndrome), D82.1 (Di George's

syndrome), D82.4 (hyperimmunoglobulin E syndrome), D83.0 (common variable immunodeficiency with predominant abnormalities of B-cell numbers and function), D83.1 (common variable immunodeficiency with predominant immunoregulatory T-cell disorders), D83.2 (common variable immunodeficiency with autoantibodies to B- or T-cells), D83.8 (other common variable immunodeficiencies), D83.9 (common variable immunodeficiency, unspecified), G11.3 (cerebellar ataxia with defective DNA repair).

Authorization of 3 months may be granted for treatment of chronic inflammatory demyelinating polyneuropathy when the following criteria are met:

A. The request is for Hizentra or Hyqvia and the requested drug will be administered in the home.
B. The treating practitioner has determined that administration of Hizentra or Hyqvia in the member's home is medically necessary and appropriate.
C. The member has a diagnosis of chronic inflammatory demyelinating polyneuropathy (ICD code G61.81).

IV. CRITERIA FOR INITIAL APPROVAL

A. Primary immunodeficiency

Initial authorization of 6 months may be granted for members with primary immunodeficiency.

B. Myasthenia gravis

1. Authorization of 1 month may be granted to members who are prescribed IG for worsening weakness, acute exacerbation, or in preparation for surgery.
    a. Worsening weakness includes an increase in any of the following symptoms: diplopia, ptosis, blurred vision, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), difficulty chewing, impaired respiratory status, fatigue, and limb weakness. Acute exacerbations include more severe swallowing difficulties and/or respiratory failure
    b. Pre-operative management (e.g., prior to thymectomy)
2. Authorization of 6 months may be granted to members with refractory myasthenia gravis who have tried and failed 2 or more standard therapies (e.g., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, rituximab).

C. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Authorization of 3 months may be granted for treatment of chronic inflammatory demyelinating polyneuropathy.

D. Dermatomyositis or Polymyositis

Authorization of 3 months may be granted when the following criteria are met:

1. Member has at least 4 of the following:
    a. Proximal muscle weakness (upper or lower extremity and trunk)
    b. Elevated serum creatine kinase (CK) or aldolase level
    c. Muscle pain on grasping or spontaneous pain
    d. Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials)
    e. Positive for anti-synthetase antibodies (e.g., anti-Jo-1, also called histadyl tRNA synthetase)
    f. Non-destructive arthritis or arthralgias
    g. Systemic inflammatory signs (fever: more than 37°C at axilla, elevated serum CRP level or accelerated ESR of more than 20 mm/h by the Westergren method),
    h. Pathological findings compatible with inflammatory myositis (inflammatory infiltration of skeletal evidence of active regeneration may be seen), and
2. Standard first-line treatments (corticosteroids) and second-line treatments (immunosuppressants) have been tried but were unsuccessful or not tolerated, or
3. Member is unable to receive standard first-line and second-line therapy because of a contraindication or other clinical reason.

E. Idiopathic Thrombocytopenic Purpura (ITP)/Immune Thrombocytopenia

1. Newly diagnosed ITP (diagnosed within the past 3 months) or initial therapy: authorization of 1 month may be granted when the following criteria are met
    a. Children (< 18 years of age)
        i. Significant bleeding symptoms (mucosal bleeding or other moderate/severe bleeding) or

ii. High risk for bleeding* (see Appendix B), or
iii. Rapid increase in platelets is required* (e.g., surgery or procedure)

b. Adults (≥ 18 years of age)
i. Platelet count < 30,000/mcL, or
ii. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required*, and
iii. Corticosteroid therapy is contraindicated and IG will be used alone or IG will be used in combination with corticosteroid therapy

2. Chronic/persistent ITP (≥ 3 months from diagnosis) or ITP unresponsive to first-line therapy: authorization of 6 months may be granted when the following criteria are met:
   a. Platelet count < 30,000/mcL, or
   b. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding* or rapid increase in platelets is required*, and
   c. Relapse after previous response to IG or inadequate response/intolerance/contraindication to corticosteroid or anti-D therapy
3. Adults with refractory ITP after splenectomy: authorization of 6 months may be granted when either of the following criteria is met:
   a. Platelet count < 30,000/mcL, or
   b. Significant bleeding symptoms
4. ITP in pregnant women: authorization through delivery may be granted to pregnant women with ITP.

* The member's risk factor(s) for bleeding (see Appendix B) or reason requiring a rapid increase in platelets must be provided.

F. B-cell chronic lymphocytic leukemia (CLL)

Authorization of 6 months may be granted for treatment of B-cell chronic lymphocytic leukemia (CLL) when all of the following criteria are met:
1. IG is prescribed for prophylaxis of bacterial infections.
2. Member has a history of recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.
3. Member has a pretreatment serum IgG level <500 mg/dL.

G. Bone marrow transplant/hemopoietic stem cell transplant (BMT/HSCT)

Authorization of 6 months may be granted to members who are BMT/HSCT recipients when the following criteria are met:
a. Therapy will be used to prevent the risk of acute graft-versus-host disease, associated interstitial pneumonia (infectious or idiopathic), septicemia, and other infections (e.g., cytomegalovirus infections [CMV], recurrent bacterial infection).
b. Either of the following:
   i. IG is requested within the first 100 days post-transplant.
   ii. Member has a pretreatment serum IgG < 400 mg/dL

H. Multifocal Motor Neuropathy (MMN)

Authorization of 3 months may be granted for treatment of multifocal motor neuropathy when the following criteria are met:
1. Member experienced progressive, multifocal, asymmetrical weakness without objective sensory loss in 2 or more nerves for at least 1 month
2. The diagnosis was confirmed by electrodiagnostic studies

I. Guillain-Barre syndrome (GBS)

Authorization of 1 month total may be granted for GBS when the following criteria are met:
1. Member has severe disease with significant weakness (e.g., inability to stand or walk without aid, respiratory weakness)
2. Onset of neurologic symptoms occurred less than 4 weeks from the anticipated start of therapy

J. Lambert-Eaton myasthenic syndrome (LEMS)

Authorization of 6 months may be granted for LEMS when the following criteria are met:
1. Diagnosis has been confirmed by either of the following:
   a. Neurophysiology studies (e.g., electromyography)

b. A positive anti- P/Q type voltage-gated calcium channel antibody test
2. Anticholinesterases (e.g., pyridostigmine) and amifampridine (e.g., 3,4-diaminopyridine phosphate, Firdapse) have been tried but were unsuccessful or not tolerated
3. Weakness is severe or there is difficulty with venous access for plasmapheresis

K. Kawasaki syndrome

Authorization of 1 month may be granted for treatment of Kawasaki syndrome in pediatric patients.

L. Stiff-person syndrome

Authorization of 6 months may be granted for stiff-person syndrome when the following criteria are met:
1. Diagnosis has been confirmed by anti-glutamic acid decarboxylase (GAD) antibody testing
2. Member had an inadequate response to first-line treatment (benzodiazepines and/or baclofen)

M. Moderate and severe immune checkpoint inhibitor-related toxicities

Authorization of 1 month may be granted for management of immune checkpoint-inhibitor toxicities when all of the following criteria are met:
1. Member has experienced a moderate or severe adverse event to a PD-1 or PD-L1 inhibitor (e,g., pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab)
2. The offending medication has been held or discontinued
3. Member experienced one or more of the following nervous system adverse events: myocarditis, bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, myasthenia gravis, peripheral neuropathy, encephalitis, transverse myelitis, severe inflammatory arthritis, Guillain-Barre syndrome, or steroid-refractory myalgias or myositis

N. Acute disseminated encephalomyelitis

Authorization of 1 month may be granted for acute disseminated encephalomyelitis in members who have had an insufficient response or a contraindication to intravenous corticosteroid treatment.

O. Autoimmune mucocutaneous blistering disease

Authorization of 6 months may be granted for treatment of biopsy proven autoimmune mucocutaneous blistering diseases when all of the following criteria are met:
1. Member has one of the following diagnoses: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (cicatricial pemphigoid), or epidermolysis bullosa acquisita.
2. At least one of the following criteria is met regarding prior treatment with conventional therapy:
   a. Member has failed conventional therapy
   b. Member has a contraindication to conventional therapy
   c. Member has rapidly progressive disease and a clinical response could not be affected quickly enough using conventional agents, and IG will be given in combination with conventional treatment.
3. IG will be used for short-term control of the member's condition and will not be used as maintenance therapy.

P. Autoimmune hemolytic anemia

Authorization of 6 months may be granted for treatment of autoimmune hemolytic anemia in members who do not respond or have a contraindication to corticosteroids or splenectomy.

Q. Autoimmune neutropenia

Authorization of 6 months may be granted for treatment of autoimmune neutropenia where treatment with G-CSF (granulocyte colony stimulating factor) is not appropriate.

R. Acquired Thrombocytopenia

Authorization of 1 month may be granted for acquired thrombocytopenia.

S. Prevention of bacterial infections in patients with multiple myeloma

Authorization of 6 months may be granted for multiple myeloma in members who have recurrent, serious infections despite the use of prophylactic antibiotics.

T. Japanese encephalitis virus disease
Authorization of 1 month may be granted for Japanese encephalitis virus disease

U. Measles (Rubeola) prophylaxis
Authorization of 1 month may be granted for postexposure prophylaxis to prevent or modify symptoms of measles (rubeola) in susceptible members exposed to the disease less than 6 days previously.

V. Multiple sclerosis
Authorization of 6 months may be granted for treatment of relapsing-remitting multiple sclerosis (RRMS).

W. Stevens-Johnson syndrome
Authorization of 1 month may be granted for severe cases of Stevens-Johnson syndrome

X. Tetanus treatment and prophylaxis
Authorization of 1 month may be granted for treatment or postexposure prophylaxis of tetanus as an alternative when tetanus immune globulin (TIG) is unavailable.

Y. Toxic epidermal necrolysis
Authorization of 1 month may be granted for severe cases of toxic epidermal necrolysis

Z. Toxic shock syndrome
Authorization of 1 month may be granted for staphylococcal or streptococcal toxic shock syndrome when the infection is refractory to several hours of aggressive therapy, an undrainable focus is present, or the member has persistent oliguria with pulmonary edema.

AA. Systemic lupus erythematosus (SLE)
Authorization of 6 months may be granted for severe, active SLE in members who have experienced inadequate response, intolerance or have a contraindication to first and second line therapies (e.g., hydroxychloroquine, glucocorticoids, anifrolumab, rituximab).
.

BB. Toxic Necrotizing Fasciitis Due To Group A Streptococcus
Authorization of 1 month may be granted for members with fasciitis due to invasive streptococcal infection

CC. Varicella prophylaxis
Authorization of 1 month may be granted for postexposure prophylaxis of varicella in susceptible individuals when varicella-zoster immune globulin (VZIG) is unavailable.

DD. Other indications
Authorization of 6 months may be granted for the following indications:
1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy or CAR-T therapy
2. Antiphospholipid syndrome
3. Asthma
4. Cerebellar ataxia due to Epstein-Barr virus infection
5. Clostridium difficile colitis
6. Adjunct to Crohn's disease treatment
7. Cytomegalovirus treatment and prophylaxis when the member is undergoing a transplant
8. Desensitization therapy – heart transplant
9. Diabetic amyotrophy
10. Hopkins' syndrome
11. Prophylaxis of enteritis due to rotavirus
12. Epilepsy
13. Fetal or neonatal thrombocytopenia
14. Gastroenteritis
15. Granulomatosis with polyangiitis
16. Hemolytic disease of fetus or newborn due to RhD isoimmunization
17. Hemophagocytic syndrome

18. Induction of Factor VIII immune tolerance
19. Herpes gestationis
20. Prevention of bacterial infections in HIV infected patients
21. Prevention of bacterial infections in post-surgical or ICU patients
22. Isaacs syndrome
23. Severe IgA nephropathy
24. Linear IgA dermatosis
25. Lysinuric protein intolerance
26. Myocarditis
27. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
28. Neonatal jaundice
29. Otitis media
30. Paraneoplastic visual loss
31. Polyarteritis nodosa
32. Post-transplant lymphoproliferative disorder
33. Pure red cell aplasia
34. Pyoderma gangrenosum
35. Renal transplant rejection
36. Respiratory syncytial virus infection
37. Sepsis
38. Systemic onset juvenile chronic arthritis
39. Systemic vasculitis
40. Heart transplant rejection
41. Desensitization of highly sensitized patients awaiting renal transplantation
42. Uveitis
43. Von Willebrand disorder

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Acquired Thrombocytopenia, Acute disseminated encephalomyelitis, Guillan-Barre syndrome, Japanese encephalitis virus disease, Kawasaki syndrome, Measles prophylaxis, Moderate and severe immune checkpoint inhibitor-related toxicities, Steven's Johnson syndrome, Tetanus treatment and prophylaxis, Toxic epidermal necrolysis, Toxic shock syndrome, Toxic Necrotizing Fasciitis Due To Group A Streptococcus, Varicella prophylaxis
Authorization for members who are requesting authorization for continuation of therapy of IG must meet all initial authorization criteria.

B. Primary Immune Deficiency
Authorization of 12 months may be granted when ALL of the following criteria are met:
1. The member is currently receiving therapy with IG
2. The member is receiving benefit from therapy, such as a reduction in the frequency of infections, improvement in disability, stabilization of condition.

C. All other indications
Authorization of 6 months may be granted when ALL of the following criteria are met:
1. The member is currently receiving therapy with IG
2. IG is being used to treat an indication enumerated in Section III
3. The member is receiving benefit from therapy, such as a reduction in the frequency of infections, improvement in disability, stabilization of condition.

VI. APPENDICES

Appendix A: Impaired Antibody Response to Pneumococcal Polysaccharide Vaccine

- Age 2 years and older: impaired antibody response demonstrated to vaccination with a pneumococcal polysaccharide vaccine
- Not established for children less than 2 years of age
- Excludes the therapy initiated in the hospital setting

Appendix B: Examples of Risk Factors for Bleeding (not all inclusive)

- Undergoing a medical or dental procedure where blood loss is anticipated
- Comorbidity (e.g., peptic ulcer disease, hypertension)
- Mandated anticoagulation therapy
- Profession or lifestyle predisposes patient to trauma (e.g., construction worker, fireman, professional athlete)

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Cutaquig, Cuvitru, Hizentra, HyQvia, and Xembify.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Chronic lymphocytic leukemia/Small lymphocytic lymphoma
4. NCCN Guideline: Management of immunotherapy-related toxicities
5. Update on the use of immunoglobulin in human disease: a review of evidence by Work Group Report of the American Academy of Allergy, Asthma, and Immunology.
6. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services.
7. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective.
8. Guidelines on the use of intravenous immune globulin for neurologic conditions.
9. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee.
10. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases.
11. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.
12. Guidelines on the use of intravenous immune globulin for hematologic conditions.
13. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency
14. Practice parameter for the diagnosis and management of primary immunodeficiency.
15. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest section of the American Academy of Allergy, Asthma and Immunology.
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28. British Society for Rheumatology guideline on management of systemic lupus erythematosus in adults
29. Guidelines on the use of intravenous immune globulin for hematologic conditions.
30. Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care.
31. European Guidelines (S1) on the use of high-dose intravenous immunoglobulin in dermatology
32. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock
33. British Association of Dermatologists' guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people
34. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus.
35. NCD 250.3: Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cutaquig, Cuvitru, Hizentra, and HyQvia, and Xembify are covered in addition to the following:

1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy
2. Acquired thrombocytopenia
3. Antiphospholipid syndrome
4. Asthma
5. Autoimmune hemolytic anemia
6. Autoimmune neutropenia
7. Bone marrow transplant/hematopoietic stem cell transplant
8. Cerebellar ataxia due to Epstein-Barr virus infection
9. Clostridium difficile colitis
10. Adjunct to Crohn’s disease treatment
11. Cytomegalovirus treatment and prophylaxis
12. Desensitization therapy – heart transplant
13. Dermatomyositis
14. Diabetic amyotrophy
15. Hopkins’ syndrome
16. Acute disseminated encephalomyelitis
17. Prophylaxis of enteritis due to rotavirus
18. Epilepsy
19. Gastroenteritis
20. Granulomatosis with polyangiitis
21. Guillain-Barre syndrome
22. Hemolytic disease of fetus or newborn due to RhD isoimmunization, prophylaxis
23. Hemophagocytic syndrome
24. Induction of Factor VIII immune tolerance
25. Measles (Rubeola) prophylaxis
26. Moderate and severe immune checkpoint inhibitor-related toxicities
27. Hypogammaglobulinemia from CAR-T therapy
28. Herpes gestationis
29. Prevention of bacterial infections in HIV infected patients
30. Prevention of bacterial infections in post-surgical or ICU patients
31. Isaacs syndrome
32. Japanese encephalitis virus disease
33. Severe IgA nephropathy

34. Lambert-Eaton myasthenic syndrome
35. Linear IgA dermatosis
36. Lysinuric protein intolerance
37. Prevention of bacterial infections in patients with multiple myeloma
38. Multiple sclerosis
39. Myasthenia gravis
40. Myocarditis
41. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
42. Neonatal jaundice
43. Otitis media
44. Paraneoplastic visual loss
45. Polyarteritis nodosa
46. Polymyositis
47. Post-transplant lymphoproliferative disorder
48. Pure red cell aplasia
49. Pyoderma gangrenosum
50. Renal transplant rejection
51. Respiratory syncytial virus infection
52. Sepsis
53. Stevens-Johnson syndrome
54. Stiff-person syndrome
55. Systemic lupus erythematosus
56. Systemic onset juvenile chronic arthritis
57. Systemic vasculitis
58. Tetanus treatment and prophylaxis
59. Fetal or neonatal thrombocytopenia
60. Toxic epidermal necrolysis
61. Toxic necrotizing fasciitis
62. Toxic shock syndrome
63. Heart transplant rejection
64. Desensitization of highly sensitized patients awaiting renal transplantation
65. Uveitis
66. Varicella prophylaxis
67. Von Willebrand disorder
68. Idiopathic thrombocytopenic purpura (ITP)
69. Multifocal motor neuropathy
70. Kawasaki syndrome
71. B-cell chronic lymphocytic leukemia (CLL)

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.
This policy considers subcutaneous administration of immune globulin as an alternative to intravenous therapy and intramuscular therapy in members who meet medical necessity criteria for intravenous immune globulin or intramuscular immune globulin.

Support for using immune globulin to treat acquired thrombocytopenia can be found in a several small studies. Hartert and colleagues reported that intravenous immune globulin provided a sustained response in a man with severe thrombocytopenia following a mismatched, related allogeneic stem cell transplant (SCT). Nine months after SCT, the man presented with papular cutaneous lesions, diarrhea, and pancytopenia. Tests for cytomegalovirus were positive. Within a few days he developed fever, arthralgia, severe pancytopenia, generalized edema, polyserositis with pericardial and pleural effusions, and nephrotic syndrome. Skin and bowel symptoms were interpreted as graft-versus-host disease. Anemia was refractory to red cell transfusion. Autoantibody testing suggested a lupus-like syndrome. He was treated with prednisolone and mycophenolate mofetil (MMF) before IVIG treatment was begun at 0.4 mg/kg on 5 consecutive days. A total of 4 cycles were given. At 2 months after symptom onset, his renal function had improved, and body weight had normalized. Hemoglobin (Hb) and platelet count were still low at the time of discharge, but there were no clinical signs of anemia or bleeding. Several weeks later, the patient was readmitted with arthralgia and decreases in platelet

count and Hb associated with a slight reduction in steroid therapy. Cytomegalovirus tests were again positive, and he was treated with foscarnet and ganciclovir. IVIG was given at 0.4 mg/kg for 5 days, resulting in a marked increase in platelet count. Hb rose slowly after discharge. IVIG was repeated 2 weeks later at a reduced dose of 5 g/day for 5 days and repeated every 4 weeks thereafter. Hb stabilized at greater than 9 g/dL, and the platelet count was maintained at greater than 80 x 10(9)/liter. The patient had no signs of graft-versus-host disease. He continued immunosuppressive therapy with prednisolone 3 mg/day and MMF 750 mg/day.
Chute et al treated trimethoprim-sulfamethoxazole thrombocytopenia in a 21-year-old patient with intravenous immune globulin (IVIG) treatment. The patient did not respond to methylprednisolone and was treated with IVIG 0.4 g/kg and a platelet transfusion. Within 1 hour, resolution of the acutely progressive disorder was measured. The proposed mechanism is an immunoglobulin-mediated reticuloendothelial Fc receptor blockade.
Guzzi et al used IVIG 0.2 g/kg for 7 days, in combination with corticosteroids, to treat secondary thrombocytopenia to sarcoidosis in a 22-year-old male. Corticosteroids alone were not effective; the platelet count did not increase substantially until IV immune globulin was added to therapy.

Support for using immune globulin to treat antiphospholipid syndrome can be found in a study by Gordon and Kilby. Therapy with intravenous immune globulin 2 g/kg in divided doses over 2 to 5 days resulted in marked clinical benefits in 4 pregnant patients (including one twin pregnancy) who developed, in the second half of pregnancy, intrauterine growth restriction (IUGR) associated with systemic lupus erythematosus and/or antiphospholipid syndrome. There were 2 early date fetal deaths. All pregnant patients had been receiving aspirin and high-dose subcutaneous heparin in the second trimester.

Support for using immune globulin to treat asthma can be found in a study by Salmun et al. Therapy with intravenous immune globulin (IVIG) 400 mg/kg every 3 weeks significantly decreased the oral steroid required by 9 patients with severe asthma that participated in a double-blind, placebo-controlled, randomized trial over 9 months. The median oral steroid required after IVIG went down to 3 mg/day from a median dose of 16.4 mg/day before IVIG treatment (p=0.0078).
Mazer and Gelfand investigated the use of IVIG in pediatric patients with asthma. Immune globulin was found to reduce the dose of corticosteroids needed and improve pulmonary function tests and symptoms in 8 children with asthma. The dose of immune globulin was 1 g/kg/day for 2 consecutive days repeated every 4 weeks for 6 months.

Support for using immune globulin to treat autoimmune hemolytic anemia can be found in a study by Flores et al (1993). Of 72 patients with warm-antibody autoimmune hemolytic anemia, approximately 40% responded to intravenous immune globulin (IVIG) treatment. Those with hepatomegaly and a low pretreatment hemoglobin had the best response to IVIG. The investigators suggest IVIG as adjunctive treatment only in select cases.

Support for using immune globulin to treat autoimmune neutropenia can be found in guidelines for the use of intravenous immune globulin for hematologic conditions from the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services. In general, immune globulin is not recommended for routine care but can be used in life-threatening circumstances.

Support for using immune globulin in patients who have received bone marrow transplants or hematopoietic stem cell transplants can be found in several published studies. A meta-analysis published by Bass et al (1993) found IVIG prophylaxis was associated with a significant reduction in posttransplant complications. Winston et al (1993) found IVIG reduces the incidence and severity of graft versus host disease. The recommended dose of immune globulin is 500 mg/kg IV 7 days and 2 days before transplantation, then weekly for 90 days following the transplant. Abdel-Mageed and colleagues (1999) conducted a comparison of two doses of intravenous immune globulin (IVIG), 250 mg/kg or 500 mg/kg given weekly from day -8 to day +111, the higher dose was associated with less acute graft-versus-host disease (p=0.03).

Support for using immune globulin to treat cerebellar ataxia due to Epstein-Barr infection can be found in a study by Daaboul, Vern, and Blend (1998). Intravenous immune globulin (IVIG) dosed at 2 g/kg over 3 days (total 144 g) may have contributed to the recovery of a 19-year-old male with acute post-infectious (Epstein-Barr virus or EBV) cerebellar ataxia. The patient presented with nausea, vomiting, unsteady gait and cervical lymphadenopathy. The presence of anti-EBV capsid IgM antibody, elevated serum EBV IgG antibody and cerebellar hyperperfusion on single-photon emission tomography led to the diagnosis. Within 2 weeks of empiric initiation of IVIG therapy, the patient recovered completely.

Support for using immune globulin to treat clostridium difficile colitis can be found in a study by Leung et al. Intravenous immune globulin was shown to be effective in preventing recurrence of colitis induced by Clostridium difficile toxin in 5 children. C difficile produces 2 types of exotoxin: toxin A and toxin B; toxin A produces diarrhea. These children, with chronically recurrent C difficile-induced colitis were found to have lower circulating levels of antitoxin A immunoglobulins than normal subjects. Administration of IV immune globulin 400 mg/kg every 3 weeks promoted resolution of gastrointestinal symptoms of colitis in all patients. However, colitis recurred in 1 patient after discontinuing the IV immune globulin; therapy was not interrupted in the other patients.

Support for using immune globulin as an adjunct to Crohn's disease treatment can be found in a study by Knoflach, Muller, and Eible (1990). The study reported transient improvement in the symptoms of Crohn disease in six patients after administration of IV immune globulin 400 mg/kg/day for 5 days. A reduction in abdominal pain and loss of fever was obtained in all patients, in 2 to 3 days after treatment. However, three patients relapsed after 2 weeks and required an additional course of immune globulin.

Support for using immune globulin to treat cytomegalovirus infection and as prophylaxis against cytomegalovirus infection can be found in two meta-analyses conducted by Glowaki (1994) and Ratko (1995). The use of intravenous immune globulin (IVIG) as passive immunization for the prevention of symptomatic cytomegalovirus disease in the transplant population.

Support for using immune globulin as desensitization therapy in patients undergoing a heart transplant can be found in guidelines published by the Canadian Cardiovascular Society/Canadian Cardiac Transplant Network. Immune globulin, targeted B cell (rituximab), and plasma cell therapies (bortezomib) form the foundation of desensitization treatments. Immunoglobulin and rituximab have increased transplantation rates, reduced wait list time, and reported graft outcomes similar to those of non-sensitized patients. However, there are no randomized trials on efficacy of desensitization therapy in heart transplant.

Support for using immune globulin to treat dermatomyositis can be found in a guideline published by the European Dermatology Forum/European Academy of Dermatology and Venereology. High dose IVIG is indicated in all severe forms of dermatomyositis. Immune globulin should generally be used as adjunctive therapy.

Support for using immune globulin to treat diabetic amyotrophy can be found in a case report by Ogawa et al. Treatment with immune globulin (IVIG) restored the ability to walk in a 49-year-old woman with diabetic amyotrophy (DA) of the thighs. The woman did not receive antidiabetic treatment for 14 years after diagnosis of diabetes mellitus. Three years after starting treatment, she began hemodialysis because of the diabetic nephropathy. A year later she began noticing weakness and atrophy of both thighs, though without pain or sensory disturbance, and she began to walk with a cane. In a short time, she became confined to a wheelchair and was diagnosed with DA. Treatment with an aldose reductase inhibitor and vitamin B12 were ineffective. She was given a 3-day course of IVIG 400 mg/kg/day (a reduced dose because of concern for congestive heart failure). On the following day, she could walk with a cane. Four weeks later she was given a second course of IVIG. Three days later she could walk unassisted. Follow-up needle electromyography suggested inactivation of proximal neuropathy. The patient experienced no adverse effects.

Support for using immune globulin to treat Hopkin's syndrome can be found in a case report published by Cohen et al (1998). A 15-year-old child experienced near complete recovery of muscle paralysis and atrophy after treatment with IV gamma globulin. Patient was diagnosed with poliomyelitis-like syndrome after an asthmatic attack. Moderate improvement in muscle strength was seen 3 weeks after patient received IV gamma globulin 1 g/kg/day for 2 consecutive days. A second treatment course was given 3 weeks later. Two years later this patient reported minimal weakness of the left deltoid muscle and he is able to play basketball.

Support for using immune globulin to treat acute disseminated encephalomyelitis (ADEM) can be found in a case series by Nishikawa et al (1999). Intravenous immune globulin (IVIG) 400 mg/kg/day for 5 consecutive days was effective in the treatment of 3 pediatric cases (ages 2 to 5 years) of ADEM. Signs and symptoms included fever, headache, vomiting and somnolence with elevated myelin basic protein in the cerebrospinal fluid (CSF) and increased signal intensity (white matter lesions) on T2-weighted magnetic resonance imaging. Each patient recovered fully within 1 to 3 weeks of IVIG therapy. Although corticosteroids have been the drug of choice for ADEM, they should be avoided in viral encephalitis. Therefore, the authors recommend IVIG therapy for suspected ADEM, reserving steroids for those who fail IVIG.

Support for using immune globulin as prophylaxis against enteritis due to rotavirus can be found in a study by Barnes et al. During the first week of life, 75 low-birth-weight neonates received oral human IgG or placebo with each feeding. IgG or placebo was given in doses of 4 mL 4 times daily during the first 7 days of life starting with the first feeding following birth. Each 4 mL of IgG contained approximately 500 mg of IgG. Twenty-five of 75 babies excreted rotavirus during the first 2 weeks of life. In babies with rotavirus, IgG was associated with delayed excretion of rotavirus and with milder symptoms of the infection. Six of 11 babies given placebo and 1 of 14 babies given IgG required low lactose feeds to alleviate rotavirus associated diarrhea. Oral human IgG protects low-birth-weight infants from diarrhea caused by rotavirus, especially in infants unprotected by other means (i.e., breastfeeding, rooming in).

Support for using immune globulin to treat epilepsy can be found in a study by Ariizumi et al. High doses of an immune globulin preparation (97% IgG and 3% IgA) were effective in producing complete clinical and electroencephalogram remission in 4 of 8 children with intractable epilepsy with attacks for 2 years or less. The probability of a successful response appeared to correspond to a short duration of illness and low serum IgA level.

Support for using immune globulin to treat gastroenteritis can be found in a study by Guarino et al. A prospective, double-blind placebo-controlled trial was conducted in 98 children with gastroenteritis (mean age 15 months +/- 8 months). Children randomized to receive a single oral dose of intravenous immune globulin (IVIG) 300 mg/kg had significantly faster improvement in stool pattern and clinical symptomatology than those receiving placebo (duration of diarrhea was 76 vs 131 hours in the placebo groups; hospital stay was 4 days in the IVIG group and 6 days in the placebo group.

Support for using immune globulin to treat granulomatosis with polyangiitis can be found in a guideline published by Groh et al. IVIG can be considered as second-line therapy for patients on glucocorticoids with or without other immunosuppressants with EGPA flares refractory to other treatments or during pregnancy. In the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections, immune globulin replacement may be considered.

Support for using immune globulin to treat Guillain-Barre syndrome can be found in two published studies. Intravenous immune globulin (IVIG) was at least as effective as plasma exchange (PE) in altering the course of Guillain-Barré syndrome (GBS) (van der Meche, 1994). One hundred forty-seven patients who were unable to walk 10 meters independently, were randomized to receive either PE (200 mL/kg in 5 sessions) over 7 to 14 days or IVIG (0.4 g/kg/day) for 5 days. In 12 patients, 1 session or more of PE had to be discontinued due to hypotension and problems with venous flow; 1 patient required discontinuation due to transient elevation of liver enzymes. In the PE group 34% of patients improved 1 functional grade or more after 4 weeks, compared with 53% in the IVIG group. This was a statistically significant difference. The median time to improvement of at least one grade was quicker in the IVIG group (27 days) when compared to the PE group (41 days). This was also a statistically significant difference. Sixty-eight complications occurred in the PE group and 39 in the IVIG group (eg, 27% of the IVIG patients required artificial ventilation in the second week vs 42% of the PE group. The investigators conclude that IVIG is at least as effective as PE.
Intravenous immune globulin (IVIG) therapy produced similar results as plasma exchange (PE) in a multicenter, randomized, controlled trial of 225 patients with Guillain-Barré syndrome conducted by the Plasma/Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. When IVIG was combined with PE therapy, results were similar compared to PE or IVIG therapy alone. All patients, regardless of the treatment regimen received, exhibited similar ability to walk unaided, median times to hospital discharge and return to work, and ability to walk at 48 weeks after therapy. Patients in the study who had a longer delay from onset to randomization had significantly more improvement after 4 weeks than those with short delays (p less than 0.001). Patients received 5 or 6 PEs of 50 mL/kg; IVIG (Sandoglobulin(R)) was dosed at 0.4 g/kg/day for 5 days.

Support for using immune globulin as prophylaxis against hemolytic disease of fetus or newborn due to RhD isoimmunization can be found in a study by de la Camara et al. IV immune globulin was effective as prenatal therapy following severe Rh immunization, improving the outcome of pregnancy, in two patients.

Support for using immune globulin to treat hemophagocytic syndrome can be found in a study by Freeman et al. Three pediatric patients with hemophagocytic syndrome were successfully treated with intravenous immune globulin (IVIG) 1 g/kg followed by packed RBCs. All patients had significant increases in their RBC counts and

decreasing tissue enzyme values soon after infusion. While some investigators caution that IVIG should not be considered sole therapy for hemophagocytic syndrome, successful treatment of a 4 1/2-year-old patient with IVIG has also been reported.

Support for using immune globulin to induce factor VIII immune intolerance can be found in a study by Nilsson et al. Successful induction of immune tolerance was achieved with a combination of factor VIII, cyclophosphamide, and high-dose IV immune globulin, in patients with hemophilia A who had developed antibodies to factor VIII. Cyclophosphamide was given from day 1 of treatment in doses of 12 to 15 mg/kg/day IV for 2 days (first dose given immediately prior to infusion of factor A), followed by oral administration of 2 to 3 mg/kg/day for 8 to 10 days. Factor VIII was given initially in doses sufficient to neutralize the inhibitor and then to raise factor VIII coagulant activity to a concentration of 40 to 100 international units/dL; factor VIII was then administered in intervals of 8 to 12 hours to maintain factor VIII coagulant activity at a level of 30 to 80 international units/dL. When decreases in factor VIII coagulant activity were observed, the daily dose of factor VIII was increased by administration of highly purified commercial virus-inactivated factor VIII concentrates at shorter intervals. Immune globulin was given initially in doses of 2.5 to 5 g IV, immediately after the first loading dose of factor VIII; beginning on day 4 of treatment, immune globulin was administered in doses of 0.4 g/kg/day for 5 days. In addition, when concentrations of factor VIII inhibitors were high initially (greater than 3 Malmo inhibitor units/mL), the antibodies were first removed by extracorporeal adsorption to protein A. With this regimen, factor VIII coagulant antibodies disappeared in 9 of 11 patients with hemophilia A following 2 to 3 weeks of combined therapy, with the half-life of infused factor VIII normalizing in 8 of these 9 patients. Stabilization of the tolerant state was observed for a median of 30 months. These data suggest that the combination of all 3 components (cyclophosphamide, factor VIII and immune globulin) are required to achieve successful induction of tolerance to factor VIII. Prior therapy in the above patients with factor VIII and cyclophosphamide and with factor VIII and immune globulin had been ineffective.

Support for using immune globulin to treat moderate and severe immune checkpoint inhibitor-related toxicities can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-Related Toxicities. The NCCN Guideline supports the use of immune globulin for the management of the below toxicities:

1. As a further intervention for myocarditis if no improvement within 24-48 hours of starting high-dose methylprednisolone
2. As an adjunct to rituximab for severe (G3) or life-threatening (G4) bullous dermatitis
3. For Stevens-Johnson syndrome, or toxic epidermal necrolysis
4. For moderate, severe, or life-threatening steroid-refractory myositis (proximal muscle weakness, neck flexor weakness, with or without myalgias) for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids
5. As treatment for severe (G3-4) myasthenia gravis
6. As treatment for moderate (G2) or severe (G3-4) Guillain-Barré Syndrome or severe (G3-4) peripheral neuropathy in combination with high-dose methylprednisolone
7. As treatment for encephalitis in combination with high-dose methylprednisolone if severe or progressing symptoms (strongly consider if progressing over 24 hours)
8. For demyelinating disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis)
9. For moderate (G3) pneumonitis if no improvement after 48-72 hours of corticosteroids or severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone

Support for using immune globulin to treat hypogammaglobulinemia from CAR-T therapy can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-Related Toxicities. The NCCN Guideline supports the use of immune globulin for the management of the below toxicities:

1. For the management of G4 cytokine release syndrome* that is refractory to high-dose corticosteroids and anti-IL-6 therapy
2. After anti-CD19 CAR T-cell therapy as replacement for hypogammaglobulinemia in select patients (those with serum IgG levels <400-600 mg/dL and serious or recurrent infections [particularly bacterial]) until serum IgG levels normalize and infections resolve

Support for using immune globulin to treat herpes gestationis can be found in a study by Harman and Black. When administered as two courses over 5 weeks, intravenous immune globulin (IVIG) 400 mg/kg/day for 5 consecutive days induced a short-term remission and decreased the autoantibody titer in a 17-year-old female who was 6 months postpartum. Intolerant to corticosteroids, the patient required cyclosporine for long-term maintenance.

Support for using immune globulin to prevent bacterial infections in HIV-infected patients can be found a report from the American Academy of Pediatrics. Intravenous immune globulin may be used for prevention of serious bacterial infections in HIV-infected pediatric patients with hypogammaglobulinemia. Use may also be considered in HIV-infected pediatric patients experiencing recurrent, serious bacterial infections (meningitis, bacteremia, pneumonia) over a 1-year period. However, in children receiving trimethoprim-sulfamethoxazole for Pneumocystis jiroveci infection (PCP) prophylaxis, IV immune globulin may not provide any additional benefit.

Support for using immune globulin to prevent bacterial infections in post-surgical or ICU patients can be found in a several studies. Siber et al conducted a double-blind, randomized, 3-arm study involving 329 ICU patients (Anon, 1992) to assess the prophylactic efficacy of hyperimmune anti-lipopolysaccharide intravenous immune globulin (IVIG) (400 mg/kg every week) or standard IVIG (400 mg/kg every week) to placebo. The adult patients were stratified by surgery type and were randomized to 1 of the 3 treatment groups. The number of patients in whom late onset infections developed was significantly lower in the standard IVIG group than in placebo (30 of 109 vs 53 of 112 patients, respectively), as was the incidence of pneumonia (15 vs 30). The number of days spent in ICU was also lower in the standard IVIG group. In contrast, the hyperimmune IVIG preparation had no detectable, prophylactic effect on infection. Investigators have commented that the inconsistent benefit of IVIG to prevent nosocomial infections is due to variable levels of antibodies in standard preparations.
Pilz and colleagues found early intravenous immune globulin (IVIG) treatment improves disease severity and may improve prognosis in prospectively score-identified high-risk postcardiac surgical patients. Patients (n=1341) at risk for sepsis after cardiac surgery were compared to 881 matched historical control patients. Patients were stratified according to risk for sepsis using a proven scoring system, APACHE (the Acute Physiology and Chronic Health Evaluation). They were treated with IVIG (Psomaglobin N: day 1 (8 mL/kg), day 2 (4 mL/kg); or Pentaglobin: days 1, 2, and 3 (5 mL/kg). Following IVIG administration, prompt and marked improvements in disease severity (i.e., a fall in APACHE score) were reported. Significantly higher score response rates, and a reduction in mortality as compared to control groups was noted, especially in the high-risk group. For the high-risk group receiving IVIG, the mean survival time of the nonsurvivors was 18.3 days as opposed to 8.3 days in the matched control group.

Support for using immune globulin to treat Isaacs syndrome can be found in a study by Ishii et al. Intravenous immune globulin (200 mg/kg/day; total 50 g) was found to worsen the symptoms of Isaac syndrome while an initial and repeat plasma exchange in a 41-year-old patient allowed symptoms to disappear for 2 to 3 weeks.

Support for using immune globulin to treat Japanese encephalitis virus disease can be found in a study by Caramello et al. In a case report, a 49-year-old man recovered from Japanese encephalitis (JE) following a 5-day course of intravenous immune globulin (IVIG). The patient was stuporose, somnolent, disoriented, febrile and had mild meningismus, photophobia and mild conjunctival hyperemia symptoms following a 3-week trip to rural Vietnam. Serologic tests via immunofluorescence were positive for JE. Saline and noncorticosteroid antiinflammatory therapy did not improve the patient's worsening confusion and agitation. On day 6 of hospitalization, a 5-day course of IVIG was initiated at 400 mg/kg, which generated symptom improvement after the first infusion. On day 23, the patient was discharged with no residual lesions and an EEG showed regression of theta-delta waves. One month later during follow-up, there was only a slight deficit in recent memory.

Support for using immune globulin to treat severe IgA nephropathy can be found in a study by Rostoker et al. A small, open prospective cohort study involving 11 patients with severe IgA nephropathy (9 with idiopathic disease and 2 with Henoch-Schonlein purpura) found a substantial decrease in proteinuria (5.2 g/day vs 2.25 g/day), hematuria and leukocyturia after intervention with IV immune globulin (2 g/kg/month x 3 months) and IM immune globulin (0.35 mL of 16.5%/kg every 15 days x 6 months). The decrease in GFR slowed or stopped and the staining intensity of glomerular IgA and C3 deposits also decreased.

Support for using immune globulin to treat lysinuric protein intolerance can be found in a case study by Dionisi-Vici et al. A 10-year-old boy with lysinuric protein intolerance, an autosomal recessive disease of defective intracellular protein transport, recovered after a single IV immune globulin dose of 1 g/kg. No relapses occurred over 2 years of follow-up.

Intravenous immunoglobulin (IVIG) has been shown to be ineffective for the prophylaxis of, and as a treatment adjunct in, infections in some high-risk, preterm, low-birth-weight neonates (USPDI, 2002). Studies published before 1990 suggested that prophylactic IVIG reduced nosocomial infections in low-birth-weight infants. However, these studies enrolled small numbers of patients; employed varied designs, preparations, and doses; and included diverse study populations. The National Institute of Child Health and Human Development (NICHHD) Neonatal Research Network therefore performed a prospective, multi-center, randomized trial to test the hypothesis that the intravenous administration of immune globulin to infants with birth weights between 501 and 1,500 grams would reduce the incidence of nosocomial infections (Fanaroff et al, 1994). In this trial, the repeated prophylactic administration of IVIG failed to reduce the incidence of nosocomial infections significantly in premature infants weighing 501 to 1,500 grams at birth. Furthermore, there were no significant differences in morbidity, mortality, or the duration of hospitalization between infants given IVIG and infants given no infusion or an infusion and placebo.

Support for using immune globulin to treat neonatal jaundice can be found in a study by Tanyer et al. Infants with isoimmune hemolytic jaundice who received multiple doses of intravenous immune globulin (IVIG) required less phototherapy than similar infants receiving a single dose or no IVIG. Sixty-one full-term babies with blood group incompatibility received multiple doses of IVIG 500 mg/kg, a single dose, or no IVIG, within 2 to 4 hours after admission for neonatal jaundice. All infants received phototherapy. Phototherapy was stopped when the bilirubin had decreased to a safe limit. In the multiple-dose group, there was no need for exchange transfusion (multiple dose vs single dose, p less than 0.05). Twelve percent of the babies in the single-dose group and 33% in the group without IVIG required exchange transfusions (p less than 0.05 and p less than 0.01, respectively compared to the multiple dose group). The duration of phototherapy was significantly less for the treated groups than for the untreated group (p less than 0.05).

Support for using immune globulin to treat otitis media can be found in a study by Ishikaza et al. Mean pneumococcal IgG and IgG2 antibody levels were significantly lower in 7 patients with recurrent acute otitis media as compared to healthy controls. They further found that following treatment with IV immune globulin (200 mg/kg every 4 weeks for 6 months), the antibody levels increased, and episodes of infection decreased. Gray conducted a 5-year, double-blind, multicenter trial. Hyperimmune bacterial polysaccharide immune globulin (BPIG) demonstrated some efficacy in children (less than 24 months) with 1 to 3 prior episodes of acute otitis media. The 76 children were randomized to receive either BPIG (0.5 mL/kg) or saline IM at entry into the study and 30 days later. During the 120-day follow-up period, the incidence of acute otitis media infections, documented by aspiration and culture of middle ear fluid, were similar in the BPIG and placebo groups. As expected, pneumococcal acute otitis media was significantly less frequent in the BPIG recipients (0.21 vs 0.45 episode/patient), and the time spent free of acute otitis media was longer in BPIG patients (51 vs 35 days). This study demonstrated that circulating antibody, even without stimulation of specific local immunity, may prevent infection of the middle ear.

Support for using immune globulin to treat paraneoplastic visual loss can be found in a study by Guy and Aptsiauri. In 2 out of 3 cases, patients with paraneoplastic visual loss benefited from intravenous immune globulin (IVIG) therapy. Marked improvement in visual acuity and visual field reported in a 62-year-old woman diagnosed with metastatic adenocarcinoma after treatment with IVIG therapy for a total dose of 2 g/kg over 5 days. Mixed results are seen in the following two cases: a 77-year-old woman presented with loss of vision on her left eye. She received IVIG 400 mg/kg over 5 days resulting in no change in light perception. A search for an occult malignant neoplasm revealed uterine cancer. A 71-year-old man diagnosed with adenocarcinoma of the pancreas with progressive loss of vision in his right eye received a dose of IVIG 400 mg/kg. He reported an improvement in the visual field defect in the right eye, with no change in visual acuity. Patient declined further treatment due to shortness of breath and itching.

Support for using immune globulin to treat polyarteritis nodosa can be found in a case report by Viguier, Guillevin and Laroche. Immune globulin therapy brought complete regression of parvovirus B19-associated polyarteritis nodosa in a 33-year-old woman. The women presented with asthenia, fever, palpable purpura, intense myalgia, paresthesias, and polyarthritis of the hand joints. Biopsies showed small- and medium-vessel vasculitis. Parvovirus B19-specific IgM and IgG antibodies and parvovirus DNA were found in serum. The patient was given IV immune globulin 1 g/kg/day for 2 days. Her condition had improved dramatically within a week, and a month later she was in complete clinical remission, although parvovirus B19 DNA was still detectable in her serum. Three years later she remained well.

Support for using immune globulin to treat polymyositis can be found in the guidelines published by European Federation of Neurological Societies (EFNS). As second-line treatment, IVIG can be considered as a treatment option in polymyositis.

Support for using immune globulin to treat post-transplant lymphoproliferative disorder can be found in a study by Cantarovich et al. Two patients recovered from post-transplantation lymphoproliferative disorder (PTLD) after receiving a combination of intravenous immune globulin (IVIG) and interferon alpha-2b. A 60-year-old female initially developed this complication 2 months after cardiac transplant. The manifestations of PTLD over the next 5 months included liver, spleen, lung and nasopharyngeal nodules. A 65-year-old male experienced onset of PTLD 8 months after liver transplant, including subQ and liver nodules. Both patients received the combination of IVIG (0.5 g/kg every 15 days) and interferon-alpha-2b (2 million units subcutaneously 3 times/week) for a total of 4 to 12 months. Their times to complete recovery from PTLD were 3 and 7 months, respectively. Corresponding lengths of remission were 47 and 33 months, respectively.

Support for using immune globulin to treat pure red cell aplasia can be found in a study by McGuire et al. Intravenous immune globulin was used to treat a 12-month-old girl with antibody-medicated pure red cell aplasia. The response was gradual with a rise in reticulocyte count from 0.1% to 3.8% at 3 weeks and a peak count of 10.5% five weeks after initiation of therapy.

Support for using immune globulin to treat pyoderma gangrenosum can be found in a study published by Herberger and colleagues. The authors observed that corticosteroids and cyclosporine A are frequently ineffective as 1st-line therapies in the treatment of pyoderma gangrenosum (PG) and associated with a number of AEs. In a retrospective, dual-center, cohort study, these investigators examined the safety and effectiveness of biologics and IVIGs in the treatment of PG. A total of 52 patients (mean age of 58.4 years) with 75 wound episodes (mean wound size of 53.2 cm^2) were included in the study. Overall, 92.3 % of patients initially received corticosteroids (CSs; 48/52); 51.9 % cyclosporine A (CSA; 27/52). In 275 therapeutic attempts, complete remission or improvement were achieved in 63.6 % (21/33) of patients on infliximab; 57.1 % (16/28) on adalimumab; 71.4 % (5/7) on etanercept; 66.6 % (6/9) on ustekinumab, and 66.7 % (10/15) of patients who were given IVIGs. That figure was 48.8 % (38/78) for those treated with CSs and 20.0 % (7/35) for individuals on CSA. On average, AEs occurred in 18.5 % (15/81) of cases treated with biologics in 20 % (3/15) of patients receiving IVIGs, in 40 % (14/35) of individuals on CSA and in 10.4 % of those treated with CSs (5/48). The authors concluded that the present retrospective analysis suggested that both biologics (especially TNF-alpha antagonists) and IVIGs are well-tolerated and safe options in the treatment of PG. Moreover, these researchers stated that data from prospective comparative studies are highly desirable.

Support for using immune globulin to treat renal transplant rejection can be found in studies that investigated IVIG as an adjunct to plasmapheresis and IVIG alone. Lerich et al conducted a single-center, retrospective analysis of all kidney and kidney-pancreas transplant recipients (n=519) that found the 2-year graft survival was 78% in 23 patients who experienced acute humoral rejection (AHR) and treated with intravenous immune globulin (IVIG) and plasmapheresis (PP) compared with 94% in 415 patients who experienced no rejection. The review identified 23 patients (mean age, 45 years) who experienced AHR (median time to AHR, 6 days; range, 5 to 8 days) that was confirmed by biopsy (C4d positive) and/or serological evidence (donor-specific anti-human leukocyte antigen antibodies). Twenty-two of these 23 patients were treated with IVIG and PP; one patient received PP alone. Other concomitant treatments were pulse methylprednisolone (n=13) and Thymoglobulin or OKT3 (n=7). The dose of IVIG widely varied but was usually 2 g/kg administered after the last PP session. The PP session varied based on urine output and serum creatinine, with most patients receiving 4 (range, 3 to 6 days) daily sessions. Posttransplant maintenance immunosuppression drugs were tacrolimus or cyclosporine, in combination with mycophenolate and prednisone. The median time to rejection was 6 days (range, 3 to 14 days, except for 2 patients with AHR at days 147 and 843, respectively). Renal function improved in 20 of 23 patients after treatment. Hemodialysis was required in 2 of the remaining 3 patients and transplant nephrectomy was subsequently performed in 2 of the 3 patients who failed to respond to treatment. The 2-year graft survival rates were 78% and 94% (p=0.0002) for the AHR and no rejection groups, respectively; the corresponding 2-year patient survival rates were 95% and 98% (p=0.09), respectively. The final mean serum creatinine levels were 1.8 mg/dL (interquartile range (IQR), 1.4 to 2.6 mg/dL) and 1.6 mg/dL (IQR, 1.3 to 1.8 mg/dL) in patients with functioning grafts for the AHR and no rejection groups, respectively. No adverse reactions were reported.
Luke et al conducted a retrospective review of 17 patients who manifested steroid-resistant or anti-lymphocyte antibody-resistant rejection of renal transplants. IVIG 2 g/kg was administered over 2 to 10 days during each treatment course, according to fluid balance status of each patient. Four patients required 2 courses of IVIG,

and 3 had 3 or more courses. IVIG , mycophenolate mofetil, and/or steroid cycle were administered in 10 patients and IVIG alone was administered to 7 patients. After a mean of 21 months after initiating IVIG , the patient survival rate was 95% and the graft survival rate was 71%. Nine of the 17 patients showed complete resolution of rejection and 5 showed reduced severity of rejection. Among the 4 patients with anti-lymphocyte antibody- resistant rejection, IVIG completely reversed rejection in 1 patient and reduced severity in 2 patients. Reduction or resolution of rejection was demonstrated in 6 of the 7 patients who received IVIG alone. In these 7 patients, the serum creatinine level was 2.2 +/- 0.9 mg/dL at baseline, 3.7 +/- 1.2 mg/dL during rejection, and 2.7 +/- 1.3 mg/dL 2 weeks after IVIG therapy.

Support for using immune globulin to treat respiratory syncytial virus infection can be found in a study by Groothuis et al. The authors conducted a multicenter, blinded, and randomized study of respiratory syncytial virus-enriched IVIG (RSVIG) in 249 infants and children. The patients were born prematurely and were less than 6 months of age at the start of the 3-year study, had bronchopulmonary dysplasia, or congenital heart disease. During the RSV season, one group received 750 mg/kg/month, a second group received 150 mg/kg/month, and the third group received no therapy. The high-dose group had significantly fewer instances of moderate to severe RSV lower respiratory tract infections (72% less), fewer hospitalizations (63% less), fewer hospital days (63% less), fewer ICU days (97% less), and less ribavirin use than did the group receiving low-dose RSVIG or no therapy. Six deaths occurred, 3 in the low- and 3 in the high-dose group. No death, however, was attributable to RSVIG or to RSV illness.

Support for using immune globulin to treat sepsis can be found in a meta-analysis by Turgeon et al. The authors conducted meta-analysis of randomized, controlled trials comparing intravenous immune globulin (IVIG) to either placebo or no intervention. IVIG significantly decreased mortality in critically ill adults with sepsis (n=2621). Based upon a pooled analysis of 20 systematically selected trials of IVIG verses either placebo or no intervention, IVIG significantly reduced mortality of adults with sepsis, severe sepsis, or septic shock (risk ratio (RR) 0.74, 95% CI, 0.62 to 0.89; p=0.001). Similar results were found in subanalysis of the peer-reviewed, published trials and the blinded trials. Sensitivity analysis revealed severity of sepsis, IVIG dose, and duration of therapy as sources of heterogeneity. Studies evaluating severely ill adults, with a diagnosis of severe sepsis or septic shock, achieved significantly greater mortality benefit from IVIG use (RR 0.64, CI, 0.52 to 0.79; p less than 0.001) versus either placebo or no intervention, whereas studies evaluating less severely ill subjects, with a diagnosis of sepsis, did not show a mortality benefit (RR 0.89, CI, 0.71 to 1.10; p=0.25). Doses of IVIG 1 g or more per kilogram showed a significant mortality benefit versus doses less than 1 g per kilogram (RR 0.61, CI, 0.4 to 0.94; p=0.02 and RR 0.79, CI, 0.64 to 0.97; p=0.08, respectively). Duration of IVIG therapy longer than 2 days significantly reduced mortality risk (RR 0.66, CI, 0.53 to 0.82; p less than 0.002); however, IVIG therapy duration of 2 days or less showed no survival benefit over either placebo or no intervention (RR 0.98, CI, 0.74 to 1.29; p=0.86). No difference was detected between the IVIG group and the placebo or no intervention group for the secondary endpoints of length of stay in the intensive care unit or duration of mechanical ventilation.
A recent guideline published by the Surviving Sepsis campaign states IV immunoglobulins are not suggested for patients with sepsis or septic shock (weak recommendation; low quality of evidence).

Support for using immune globulin to treat Stevens-Johnson syndrome and toxic epidermal necrolysis can be found in the European guidelines on the use of high-dose intravenous immunoglobulin in dermatology (Enk et al). High-dose IVIG can be considered for confirmed Stevens-Johnson syndrome and toxic epidermal necrolysis. IVIG should be given as soon as SJS/TEN is diagnosed. In contrast, the British Guidelines for the management of SJS/TEN indicates there is insufficient evidence to support or refute benefit of IVIG in this scenario (McPherson et al).

Support for using immune globulin to treat Stiff-person syndrome can be found in a study by Dalakas. Intravenous immune globulin (IVIG) reduced stiffness parameters and factors of heightened sensitivity in patients (N=16) with stiff-person syndrome unresponsive to other agents. The mean age of study participants was 47 years (9 women, 7 men). Patients were incompletely responding to therapies. At enrollment, all patients were receiving benzodiazepines, 6 were receiving baclofen, 3 gabapentin, and 1 patient was receiving valproic acid. Doses remained unchanged throughout the study. Patients were otherwise balanced with regard to disease duration, onset of symptoms, disease severity, and other associated conditions. Immune globulin 2 g/kg IV, divided in 2 daily doses, or placebo (half-normal saline) was administered every month for 3 months. After a washout period of 1 month, the patients crossed over to the alternative therapy for another 3 months. All patients were followed for at least 3 months after the infusions. The mean number of stiff areas in the placebo group remained constant during the first 4 months but then dropped significantly in the next 3 months,

after cross over. The scores of the IVIG group dropped in the first 3 months, remained constant during the wash-out period and rebounded from months 5 through 8 but never reached baseline. There was a significant difference in changes in the stiff areas between the 2 groups for the direct treatment effect on the month following each infusion and the first order carry-over effect (residual effects after 3 monthly infusions). Subanalysis of each of the stiffness areas showed a significant reduction of the stiffness in the trunk, abdomen, and the face. The duration of benefit varied from 6 to 12 weeks or up to a year. Change in the scores of distribution of stiffness index (total = 6) and heightened sensitivity (total = 7) from baseline to the 2nd and 3rd month were obtained after each treatment. The net differences in the stiffness index and heightened sensitivity scores from baseline to the end of 3 months of treatment and the first or second carry-over effects were compared between the patients randomized to the 2-treatment group for each period.

Support for using immune globulin to treat systemic lupus erythematosus can be found in the EULAR guidelines (Fanouriakis et al). Immune globulin is suggested for acute treatment of systemic lupus erythematosus-associated thrombocytopenia, as well as in cases with inadequate response to high-dose glucocorticoids, or to avoid glucocorticoid-related infections.

Support for using immune globulin to treat systemic onset juvenile chronic arthritis can be found in a study by Vignes et al. An uncontrolled pilot study (n=7) reported a 71% response rate for intravenous immune globulin (IVIG) therapy of adult onset Still disease refractory to monotherapy with nonsteroidal inflammatory agents. Patients received IVIG 2 g/kg over 2 or 5 days every 4 weeks for up to 6 cycles. Two patients did not respond to IVIG but achieved remission with oral prednisone. Of 5 responders, 1 patient relapsed after 5 months. The remaining 4 patients continued in remission for 11 to 53 months without additional IVIG.

Support for using immune globulin to treat systemic vasculitis can be found in a study by Jayne et al. IV immune globulin was effective in treating systemic vasculitis in 7 patients. Immune globulin 0.4 g/kg/day for 5 days was administered. Decreases in antineutrophil cytoplasm antibodies and C-reactive protein were observed which lasted for up to 100 days. Two of these patients had their immunosuppressive therapy discontinued prior to treatment with immune globulin, 2 other patients had not been previously treated, and the remaining patients continued other therapy during the study. The effect of immune globulin was only transient in one patient.

Support for using immune globulin to treat fetal or neonatal thrombocytopenia can be found in a study by Bussel et al. Antenatal therapy with IV immune globulin (1 g/kg over 4 to 7 hours weekly), with or without dexamethasone 3 to 5 mg daily, was reported effective in increasing fetal platelet counts in severe neonatal alloimmune thrombocytopenia. In this study, 7 pregnant women were treated with immune globulin (5 also received dexamethasone). All patients had previously had infants with severe alloimmune thrombocytopenia. Periumbilical blood sampling performed in 6 fetuses demonstrated increases in platelet counts by a mean of 72.5 x 10(9)/L. Platelet counts were above 30 x 10(9)/L at birth in all 7 treated fetuses, and no cases of intracranial hemorrhage were observed; all of the 7 infants who were untreated had lower platelet counts, with 3 developing intracranial hemorrhage (antenatal in 2 infants). Mild intrauterine growth retardation was observed in 1 treated infant (whose mother received dexamethasone concurrently), and oligohydramnios occurred in 4 dexamethasone-treated patients during the third trimester. However, all 7 infants developed normally during follow-up of 2 months to 4 years following birth. Percutaneous umbilical blood sampling should be performed at 20 to 22 weeks gestation in women who have previously delivered an infant with alloimmune thrombocytopenia and a platelet count under 30 x 10(9)/L at birth; IV immune globulin therapy is recommended weekly if the fetal platelet count drops below 100 x 10(9)/L. Sampling should be repeated 4 to 6 weeks later to evaluate effects of treatment. In the case of treatment failure, early Caesarean section is the primary alternative, although selective platelet transfusion may also have a role.

Support for using immune globulin to treat toxic necrotizing fasciitis and toxic shock syndrome can be found in a study by Darenberg et al. In a double-blind, placebo-controlled trial of 21 patients with streptococcal toxic shock syndrome caused by severe invasive group A streptococci infection, with or without necrotizing fasciitis, there was a 3.6-fold lower mortality rate at 28 days in patients receiving adjunctive therapy of intravenous immune globulin (IVIG) compared to placebo. The study randomized patients to receive either IVIG 1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3, or to the placebo group receiving 1% albumin. Adjunctive therapy consisted of clindamycin 600 mg IV 3 times daily plus benzylpenicillin 12 g/day or cefuroxime 1.5 g 3 times per day in penicillin allergic patients. The study was terminated prematurely due to slow patient recruitment. Primary endpoint analysis demonstrated the morality rate at day 28 as 1 patient in the IVIG group (n=10), and in 4 patients in the placebo group (n=11). There were no significant differences in secondary endpoint

analysis: time to resolution of shock in the survivors (mean of 88 hours vs 122 hours), or mortality at day 180 (2 vs 4 patients) in the IVIG and placebo groups, respectively.

Support for using immune globulin to treat heart transplant rejection can be found in a study by Jordan et al (1998). Rapid improvement in treating antibody-mediated allograft rejection is reported within 2 to 5 days after high-dose intravenous immune globulin (IVIG) (2 g/kg) treatment in all 10 patients in the study. IVIG also contains anti-idiopathic antibodies that are potent inhibitors of donor-specific human leukocyte antigen alloantibodies, thus preventing organ rejection episodes.

Support for using immune globulin to desensitize a highly sensitized patient awaiting renal transplantation can be found in a study by Jordan et al (2004). Successive, pretransplant treatments with high-dose intravenous immunoglobulin (IVIG) in highly sensitized patients with ESRD significantly improved the transplantation rate and time to transplantation compared with placebo in the multicenter, randomized, double-blind National Institutes of Health (NIH) IG02 trial (n=98). Highly sensitized adults (panel reactive antibody (PRA), 50% or greater every month for 3 months; mean age, 40.7 years; range, 20 to 73 years; 57% female) were randomized to receive pretransplant infusions of either IVIG 2 g/kg (maximum, 180 g; Gamimune(R) N 10% SD) (n=48; prior transplant, 73%) or placebo (n=50; prior transplant, 58%) every month for 4 months. If not transplanted after 4 months, additional infusions were given at 12 and 24 months, with follow-up until 30 months. If transplanted after 4 months, patients received additional blinded infusions monthly for 4 months. The mean PRA 1 to 3 months before study entry was approximately 80% or higher. Six patients (nonadherent group) were excluded from the analysis because they either failed to initiate therapy (n=4) or received crossover therapy (n=2; assigned to placebo but received IVIG). Among the dosing-adherent group (n=92), the transplantation rate in the IVIG group (35%; 16 of 46) was twice that in the placebo group (17%; 8 of 46) (p=0.048). Among patients who had received a previous transplant, transplantation rates were 22% (10 of 34) and 7% (3 of 28) in the IVIG and placebo groups, respectively. In addition, pretreatment with IVIG significantly reduced time to transplantation compared with placebo (p=0.049), and this improvement remained significant after adjusting for receipt of previous transplantation (p=0.034). The projected mean time to transplantation (assuming constant hazard rate) was estimated to be 4.8 years for IVIG compared with 10.3 years for placebo. Pretransplant treatment with IVIG significantly reduced mean PRA levels for IgG plus IgM (p=0.033) and IgG alone (p=0.007) relative to placebo; however, the mean PRA at each time point during the study period was greater than 40%. Notably, PRA levels returned to near baseline at 6 months following IVIG infusion. Among all transplant recipients (includes 3 patients from the nonadherent group), significantly more acute rejection episodes occurred in the IVIG group (9 of 17) than the placebo group (1 of 10) (p=0.042). However, among the dosing-adherent transplant recipients, graft failure rates during the 30-month follow-up period (25% vs 38%, respectively) and 2-year graft survival rates (80% vs 75%, respectively) were similar in the IVIG and placebo groups. Overall, IVIG was well tolerated; the incidence of headache was greater with IVIG compared with placebo (52% vs 30%).

Support for using immune globulin to treat uveitis can be found in a study by LeHoang et al. Use of intravenous immune globulin (IVIG) provided a safe and effective therapy for patients with birdshot retinochoroidopathy, a bilateral autoimmune posterior uveitis. For induction therapy, patients (n=18) received IVIG 0.4 g/kg/day for 4 days every 4 weeks for 6 months. Thereafter, patients received IVIG 1.2 to 1.6 g/kg over 2 to 4 days at 6 to 8 week intervals. Within the first 3 months, patients experienced visual field improvements and within 2 to 6 months, improvements in visual acuity and macular edema improved. After 6 months, in the 26 eyes with a visual acuity of 20/30 or less, 14 eyes improved by at least 2 lines and 2 eyes deteriorated. In 5 patients with an initial visual acuity of 20/25, visual acuity increased to 20/20 in 4 and remained unchanged in 1. In 5 eyes with an initial acuity of 20/20, 4 remained stable and 1 deteriorated. Initially macular edema was present in 23 eyes with 17 eyes showing a decrease in macular edema on fundus fluorescein angiograms after 6 months. After a mean follow-up period of 39 months, 33 out of 36 eyes continued to show improved or stable visual acuity.

Support for using immune globulin to treat von Willebrand disorder can be found in two case studies. Intravenous immune globulin (IVIG) was efficacious when administered to a 47-year-old man with acquired Von Willebrand syndrome (Hanley et al). A 5-day course of IVIG 400 mg/kg/day was administered prior to orthopedic surgery and anticoagulation treatment was continued following surgery. At 7 days following the IVIG course, there was normalization of clotting factors and von Willebrand factors/cofactors.
Sampson et al reported temporary restoration of von Willebrand factor with control of bleeding episodes in a 75-year-old man diagnosed with acquired type 2a von Willebrand disease. This patient has received repeated

treatments of intravenous immune globulin (IVIG) 30 g/day for 5 days after each bleeding episode over the past 3 years.

Pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (cicatricial pemphigoid) and epidermolysis bullosa acquisita are covered according to the conditions outlined in National Coverage Determination Manual section called Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases (250.3- Version 1).

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SUPPRELIN LA (histrelin acetate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Supprelin LA is indicated for the treatment of children with central precocious puberty (CPP).

B. Compendial Use
1. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
2. Preservation of ovarian function
3. Prevention of recurrent menstrual related attacks in acute porphyria

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

A. The following documentation must be available, upon request, for all submissions:
1. For central precocious puberty, laboratory report or medical record of a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay.

III. CRITERIA FOR INITIAL APPROVAL

A. Central precocious puberty (CPP)
1. Authorization of 12 months may be granted for treatment of CPP in a female member when all of the following criteria are met:
   i. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI]).
   ii. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay.
   iii. The assessment of bone age versus chronological age supports the diagnosis of CPP.
   iv. The member was less than 8 years of age at the onset of secondary sexual characteristics.
2. Authorization of 12 months may be granted for treatment of CPP in a male member when all of the following criteria are met:
   i. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging (e.g., CT scan, MRI).
   ii. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third generation LH assay.
   iii. The assessment of bone age versus chronological age supports the diagnosis of CPP.
   iv. The member was less than 9 years of age at the onset of secondary sexual characteristics.

B. Gender dysphoria
1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member has reached Tanner stage 2 of puberty or greater.

2. Authorization of 12 months may be granted for gender transition when all of the following criteria are met:
    a. The member has a diagnosis of gender dysphoria.
    b. The member will receive the requested medication concomitantly with gender-affirming hormones.

C. Preservation of ovarian function
Authorization of 3 months may be granted for preservation of ovarian function when the member is premenopausal and undergoing chemotherapy.

D. Prevention of recurrent menstrual related attacks in acute porphyria
Authorization of 12 months may be granted for prevention of recurrent menstrual related attacks in members with acute porphyria.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. Supprelin LA is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Supprelin LA
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology
3. Standards of Care for the Health of Transgender and Gender Diverse People
4. Endocrine Treatment of Gender Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline.
5. ACOG Health Care for Transgender and Gender Diverse Individuals

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Supprelin LA are covered in addition to gender dysphoria.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Supprelin LA to treat gender dysphoria can be found in following compendial resources and guidelines: Micromedex DrugDex, Lexi-Drugs, Standards of Care for the Health of Transgender and Gender Diverse People, ACOG Health Care for Transgender and Gender Diverse Individuals, and Endocrine Treatment of Gender Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline.
Support for using Supprelin LA for preservation of ovarian function and prevention of recurrent menstrual related attacks in acute porphyria can be found in following compendial resources and guidelines: Micromedex DrugDex, Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis, and best practice guidelines on clinical management of acute attacks of porphyria and their complications.

VII. REFERENCES

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SUSVIMO (ranibizumab injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Susvimo (ranibizumab injection) is indicated for the treatment of patients with Neovascular (wet) Age-related Macular Degeneration (AMD) who have previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Neovascular (Wet) Age-Related Macular Degeneration
Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration when all of the following criteria is met:

A. The member has a diagnosis of neovascular (wet) age-related macular degeneration.
B. The member has previously responded (in the last 6 months) to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) Inhibitor (e.g., Avastin, Eylea).
C. Must be used in conjunction with the Susvimo ocular implant.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with Susvimo
B. Susvimo is being used to treat an indication enumerated in Section II
C. The medication has been effective for treating the diagnosis or condition

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Susvimo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Susvimo are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Susvimo. [package insert]. San Francisco, CA: Genentech, Inc.; April 2022.
2. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp.

SYFOVRE (pegcetacoplan)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Syfovre is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial Requests: Chart notes or medical records confirming the diagnosis of geographic atrophy (GA) secondary to AMD.
B. Continuation Request: Chart notes or medical records confirming a positive clinical response to therapy.

III. EXCLUSION

Coverage will not be provided for the treatment of geographic atrophy (GA) secondary to a condition other than AMD (such as Stargardt disease, cone rod dystrophy, toxic maculopathies).

IV. CRITERIA FOR INITIAL APPROVAL

Geographic atrophy (GA) secondary to age-related macular degeneration
Authorization of 12 months may be granted for treatment of geographic atrophy when the member has a diagnosis of geographic atrophy secondary to age-related macular degeneration.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when ALL of the following criteria are met:
A. The member is currently receiving therapy with the requested product.
B. The requested product is being used to treat an indication enumerated in Section IV.
C. The medication has been effective for treating the diagnosis or condition (e.g., a reduction or stabilization in the rate of vision decline or the risk of more severe vision loss, stabilization or reduction in total area of GA lesions).

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Syfovre.
2. The available compendium

a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. Age-Related Macular Degeneration Preferred Practice Pattern 2019

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Syfovre are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCE

1. Syfovre [package insert]. Waltham, MA: Apellis Pharmaceuticals Inc; November 2023.
2. Age-Related Macular Degeneration PPP 2019. American Academy of Ophthalmology. Published October 2019. Accessed December 11, 2023. https://www.aao.org/education/preferred-practice-pattern/age-related-macular-degeneration-ppp

SYLVANT (siltuximab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Sylvant is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.

B. Compendial Uses
1. Relapsed/refractory unicentric Castleman's disease
2. CAR T-cell related toxicities – Cytokine release syndrome (CRS)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: medical record documentation of HIV and HHV-8 status (where applicable).

III. CRITERIA FOR INITIAL APPROVAL

A. Multicentric Castleman's disease or relapsed/refractory unicentric Castleman's disease
Authorization of 12 months may be granted for treatment of active multicentric Castleman's disease with no organ failure or relapsed/refractory unicentric Castleman's disease when all of the following criteria are met:
1. Member is human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.
2. The requested medication is used as a single agent.

B. Cytokine release syndrome
Authorization of 1 month may be granted for the treatment of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome when either of the following criteria are met:
1. Cytokine release syndrome is refractory to high-dose corticosteroids and anti-IL-6 therapy.
2. The requested medication will be used as a replacement for the second dose of tocilizumab when supplies are limited or unavailable.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat multicentric Castleman's disease or relapsed/refractory unicentric Castleman's disease
C. The member is receiving benefit from therapy. Benefit is defined as:

1. No evidence of unacceptable toxicity, AND
2. No evidence of disease progression while on current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Sylvant.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas
4. NCCN Guideline: Management of immunotherapy-related toxicities

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Sylvant are covered in addition to the following:

1. Relapsed/refractory unicentric Castleman's disease
2. CAR T-cell related toxicities – Cytokine release syndrome (CRS)

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Sylvant to treat relapsed or refractory unicentric Castleman's disease can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Sylvant to treat CAR-T cell-related toxicities can be found in the National Comprehensive Cancer Network's guideline for the Management of Immunotherapy-related Toxicities. The NCCN Guideline supports the use of Sylvant in the following scenarios:

- Management of G4 cytokine release syndrome that is refractory to high-dose corticosteroids and anti-IL-6 therapy
- As a replacement for the second dose of tocilizumab when supplies are limited or unavailable for the management of G1-G4 cytokine release syndrome or G1-G4 neurotoxicity as additional therapy if concurrent cytokine release syndrome

VII. REFERENCES

1. Sylvant [package insert]. Hemel Hempstead, Hertfordshire, U.K.: EUSA Pharma, LTD; December 2019.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 8, 2024.

SYNRIBO (omacetaxine mepesuccinate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Synribo is indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs).

B. Compendial Uses
1. Primary treatment of advanced phase CML for patients with disease progression to accelerated phase
2. Follow-up therapy for CML patients after hematopoietic stem cell transplant (HSCT)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Prior to initiation of therapy: results of cytogenetic and/or molecular testing for detection of the Ph chromosome or the BCR-ABL gene

III. CRITERIA FOR INITIAL APPROVAL

Chronic Myeloid Leukemia (CML)
Authorization of 12 months may be granted for treatment of CML confirmed by detection of the Ph chromosome or BCR-ABL gene by cytogenetic and/or molecular testing when all of the following criteria are met:
1. Member meets any of the following:
   a. Member has chronic or accelerated phase CML
   b. Member has received HSCT for CML
2. Member has experienced resistance or intolerance to two or more tyrosine kinase inhibitors (TKIs) (e.g., bosutinib, dasatinib, imatinib, nilotinib, ponatinib)
3. The requested medication is used as a single agent

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment of CML when there is no evidence of unacceptable toxicity or disease progression while on the current regimen and either of the following criteria is met:
1. Member has CML that has been confirmed by detection of Ph chromosome or BCR-ABL gene by cytogenetic and/ or molecular testing
2. Member has received HSCT for CML

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Synribo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Chronic Myeloid Leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Synribo are covered in addition to advanced phase CML with disease progression to accelerated phase and follow-up therapy for CML patients after hematopoietic stem cell transplant (HSCT).

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Synribo to treat advanced phase CML with disease progression to accelerated phase and follow-up therapy for CML patients after hematopoietic stem cell transplant (HSCT)can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Synribo [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; September 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 2023.
3. NCCN Clinical Practice Guidelines in Oncology® Chronic Myeloid Leukemia (Version 1.2024). © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed November 2023

TAKHZYRO (lanadelumab-flyo)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Takhzyro is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 2 years and older.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial authorization:
   1. C1 inhibitor functional and antigenic protein levels
   2. F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
   3. Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
B. For continuation of therapy, chart notes demonstrating a reduction in frequency of attacks

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

IV. CRITERIA FOR INITIAL APPROVAL

Hereditary angioedema (HAE)
Authorization of 6 months may be granted for prevention of HAE attacks when either of the following criteria is met at the time of diagnosis:
A. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
   1. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
   2. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
B. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
   1. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
   2. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for prevention of HAE attacks when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The member is receiving benefit from therapy. Benefit is defined as:
    1. A significant reduction in frequency of attacks (e.g., ≥ 50%) since starting treatment, and
    2. A reduction in the use of medications to treat acute attacks since starting treatment.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Takhzyro.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
4. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Takhzyro are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.
When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

VIII. REFERENCES

1. Takhzyro [package insert]. Lexington, MA: Dyax Corp., a Takeda company; February 2023.
2. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. Allergy Asthma Proc. 2012; 33(6):S145-S156.
3. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
4. Veronez CL, Csuka D, Sheik FR, et al. The expanding spectrum of mutations in hereditary angioedema. *J Allergy Clin Immunol Pract.* 2021;S2213-2198(21)00312-3.

TALVEY (talquetamab-tgvs)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Multiple Myeloma
Authorization of 12 months may be granted for treatment of relapsed or refractory multiple myeloma in members who have received at least 4 prior therapies, including at least one drug from each of the following categories:
A. Proteasome inhibitor (e.g., bortezomib, ixazomib, carfilzomib)
B. Immunomodulatory agent (e.g., lenalidomide, pomalidomide)
C. Anti-CD38 monoclonal antibody (e.g., daratumumab)

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen, and
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Talvey.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Talvey [package insert]. Horsham, PA: Janssen Biotech, Inc.; August 2023.

TECARTUS (brexucabtagene autoleucel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

1. Adult patients with relapsed or refractory mantle cell lymphoma (MCL)
2. Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

Coverage will not be provided for members less than 18 years of age.

III. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Chart notes, medical record documentation or claims history supporting previous lines of therapy.

IV. CRITERIA FOR INITIAL APPROVAL

A. Mantle Cell Lymphoma

Authorization of 3 months may be granted for treatment of mantle cell lymphoma when all of the following criteria are met:

1. The disease is relapsed or refractory.
2. The member has had previous treatment with both chemoimmunotherapy and a bruton tyrosine kinase inhibitor (e.g., ibrutinib).
3. The member does not have active hepatitis B, active hepatitis C, or any active uncontrolled infection.
4. The member does not have an active inflammatory disorder.

B. Adult Relapsed or Refractory B-cell precursor Acute Lymphoblastic Leukemia (ALL)

Authorization of 3 months may be granted for the treatment of acute lymphoblastic leukemia (ALL) when all of the following criteria are met:

1. The disease is relapsed or refractory meeting either of the following criteria:
   i. Member has Philadelphia chromosome-negative disease
   ii. Member has Philadelphia chromosome-positive disease following therapy that has included tyrosine kinase inhibitors (TKIs) (e.g., bosutinib, dasatinib, imatinib, nilotinib, ponatinib)
2. The member does not have active hepatitis B, active hepatitis C, or any active uncontrolled infection.
3. The member does not have active graft versus host disease.
4. The member does not have an active inflammatory disorder.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Tecartus.
2. The available compendium

a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Acute lymphoblastic leukemia
4. NCCN Guideline: B-cell lymphomas
5. National Coverage Determination: Chimeric Antigen Receptor (CAR) T-cell Therapy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tecartus are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

All FDA-approved indications are covered according to the conditions outlined in National Coverage Determination Manual section 110.24 (Chimeric Antigen Receptor [CAR] T-cell Therapy).

VII. REFERENCES

1. Tecartus [package insert]. Santa Monica, CA: Kite Pharma, Inc.; October 2021.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed June 6, 2023.
3. National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24-Version 1). https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=344&ncdver=1&DocID=110.22&from2=search.asp&bc=gAAAAAgAAAAA& Accessed June 9, 2023.

TECENTRIQ (atezolizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Non-small cell lung cancer (NSCLC)
   a. Tecentriq, as a single-agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test
   b. Tecentriq, as a single-agent, is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
   c. Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment, of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
   d. Tecentriq, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
   e. Tecentriq, as a single agent is, indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving the requested medication.

2. Small cell lung cancer (SCLC)
   Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

3. Hepatocellular Carcinoma (HCC)
   Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

4. Melanoma
   Tecentriq, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

5. Alveolar Soft Part Sarcoma (ASPS)
   Tecentriq, as a single agent, is indicated for the treatment of adult and pediatric patients age 2 years and older with unresectable or metastatic ASPS.

B. Compendial Uses
1. Urothelial carcinoma
2. Non-small cell lung cancer (NSCLC)
3. Mesothelioma
4. Cervical Cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Urothelial carcinoma

Authorization of 12 months may be granted for treatment of urothelial carcinoma when any of the following criteria is met:

1. Member is not eligible for cisplatin-containing chemotherapy, and the member's tumor expresses PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area).
2. Member is not eligible for any platinum containing chemotherapy.
3. The requested medication will be used for the first-line treatment of locally advanced or metastatic urothelial carcinoma in combination with gemcitabine and cisplatin or gemcitabine and carboplatin.
4. The requested medication will be used for the treatment of locally advanced or metastatic urothelial carcinoma in members with disease that has progressed during or following chemotherapy.

B. Non-small cell lung cancer (NSCLC)

1. Authorization of 12 months may be granted for treatment of recurrent, advanced or metastatic non-small cell lung cancer when there are no EGFR exon 19 deletions or L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue) and any of the following criteria are met:
   a. The requested medication will be used as continued maintenance therapy as a single agent or in combination with bevacizumab.
   b. The requested medication will be used as first line or subsequent therapy in combination with chemotherapy with or without bevacizumab.
   c. The requested medication will be used as first line therapy for PD-L1 expression positive (≥50%) tumors as a single agent.
2. Authorization of 12 months may be granted for treatment of stage II to IIIB non-small cell lung cancer that is PD-L1 positive as single agent adjuvant therapy.
3. Authorization of 12 months may be granted for treatment of recurrent, advanced or metastatic non-small cell lung cancer as single agent subsequent therapy.

C. Small cell lung cancer (SCLC)

Authorization of 12 months may be granted for treatment of small cell lung cancer when the requested medication will be used as initial treatment in combination with etoposide and carboplatin (followed by single agent maintenance) for extensive-stage disease.

D. Hepatocellular carcinoma (HCC)

Authorization of 12 months may be granted for treatment of unresectable, inoperable, metastatic, or disease with extensive liver tumor burden hepatocellular carcinoma when the requested medication will be used as initial treatment in combination with bevacizumab.

E. Melanoma

Authorization of 12 months may be granted for treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma when the requested medication is used in combination with cobimetinib and vemurafenib.

F. Mesothelioma

Authorization of 12 months may be granted for subsequent treatment of peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when used in combination with bevacizumab.

G. Alveolar Soft Part Sarcoma (ASPS)

Authorization of 12 months may be granted for the treatment of patients with unresectable or metastatic alveolar soft part sarcoma when used as a single agent.

H. Cervical Cancer

Authorization of 12 months may be granted for the treatment of persistent, recurrent or metastatic small cell neuroendocrine carcinoma of the cervix (NECC) when used in combination with etoposide and either cisplatin or carboplatin.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months (12 months total for adjuvant NSCLC) may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

1. The contents of this policy were created after examining the following resources:
2. The prescribing information for Tecentriq.
3. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
4. NCCN Guideline: Small cell lung cancer
5. NCCN Guideline: Peritoneal mesothelioma
6. NCCN Guideline: Cutaneous melanoma
7. NCCN Guideline: Non-small cell lung cancer
8. NCCN Guideline: Hepatocellular carcinoma
9. NCCN Guideline: Soft tissue sarcoma
10. NCCN Guideline: Bladder cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tecentriq are covered in addition to the following:

A. Urothelial carcinoma
B. Non-small cell lung cancer
C. Mesothelioma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Tecentriq to treat urothelial carcinoma, non-small cell lung cancer and peritoneal mesothelioma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Tecentriq to treat urothelial carcinoma can be found in the Clinical Pharmacology database. Use of information in the Clinical Pharmacology database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). The Clinical

Pharmacology database supports the use of Tecentriq as treatment of locally advanced or metastatic urothelial carcinoma.

VI. REFERENCES

1. Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc.; May 2023.
2. The NCCN Drugs & Biologics Compendium®© 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed December 13, 2023.
3. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2022- [cited December 13, 2023]. Available from: http://www.clinicalkey.com.

TECVAYLI (teclistamab-cqyv)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Tecvayli is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Multiple Myeloma
Authorization of 12 months may be granted for treatment of relapsed or refractory multiple myeloma in members who have received at least 4 prior therapies, including at least one drug from each of the following categories:
1. Anti-CD38 monoclonal antibody (e.g., daratumumab)
2. Proteasome inhibitor (e.g., bortezomib, ixazomib, carfilzomib)
3. Immunomodulatory agent (e.g., lenalidomide, pomalidomide)

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE
The contents of this policy were created after examining the following resources:
1. The prescribing information for Tecvayli.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Multiple Myeloma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Tecvayli [package insert]. Horsham, PA: Janssen Biotech, Inc.; August 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed October 2, 2023.

TEGSEDI (inotersen)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Tegsedi is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests:
   1. Testing or analysis confirming a mutation of the TTR gene
   2. Medical record documentation confirming that the member demonstrates signs and symptoms of polyneuropathy (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy)
B. For continuation requests: medical record documentation confirming the member demonstrates clinical benefit compared to baseline

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a neurologist, geneticist, or physician specializing in the treatment of amyloidosis.

IV. CRITERIA FOR INITIAL APPROVAL

Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis
Authorization of 12 months may be granted for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (also called transthyretin-type familial amyloid polyneuropathy [ATTR-FAP]) when all of the following criteria are met:
A. The diagnosis is confirmed by detection of a mutation of the TTR gene.
B. Member exhibits clinical manifestations of ATTR-FAP (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy).
C. The member is not a liver transplant recipient.
D. The requested medication will not be used in combination with patisiran (Onpattro), tafamidis (Vyndaqel, Vyndamax) or vutrisiran (Amvuttra)

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving treatment with the requested medication.

B. The requested medication is being used for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis.
C. There is a clinical benefit from therapy with the requested medication (e.g., improvement of neuropathy severity and rate of disease progression as demonstrated by the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score, the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, polyneuropathy disability (PND) score, FAP disease stage, manual grip strength).

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Tegsedi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Guideline of transthyretin-related hereditary amyloidosis for clinicians

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tegsedi are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Tegsedi and the above initial criteria can be found in the guideline from Ando and colleagues discussing hereditary transthyretin amyloidosis. The diagnosis of ATTR should be suspected in patients with progressive sensorimotor and/or autonomic neuropathy. The diagnosis of hereditary ATTR is established when characteristic clinical features are present, a biopsy showing amyloid deposits that bind to anti-TTR antibodies, and identification of mutations of the TTR gene.
The treatment for peripheral and autonomic neuropathy is orthotopic liver transplantation, TTR tetramer stabilizers and gene-silencing therapies. Liver transplantation provides a wild type gene expressing normal TTR in the liver. Successful liver transplantation results in the disappearance of the variant TTR protein and thus halts the progression of peripheral and/or autonomic neuropathy.

VIII. REFERENCES

1. Tegsedi [package insert]. Waltham, MA: Sobi, Inc.; June 2022.
2. Benson MD, et. al., Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5; 379(1):22-31.
3. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L, Planté-Bordeneuve V, Rapezzi C, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31.

Temodar (temozolomide)
temozolomide

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Newly Diagnosed Glioblastoma
      Temodar is indicated for the treatment of adult patients with newly diagnosed glioblastoma concomitantly with radiotherapy and then as maintenance treatment.

   2. Refractory Anaplastic Astrocytoma
      Temodar is indicated for the treatment of adult patients with refractory anaplastic astrocytoma who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

B. Compendial Uses
   1. Central nervous system (CNS) cancer
   2. Ewing sarcoma
   3. Neuroendocrine tumors of the pancreas, gastrointestinal tract, lung, and thymus
   4. Well-differentiated grade 3 neuroendocrine tumors
   5. Extrapulmonary Poorly differentiated (high grade) neuroendocrine carcinoma/large or small cell carcinoma
   6. Pheochromocytoma/paraganglioma
   7. Cutaneous melanoma
   8. Uveal melanoma
   9. Mycosis fungoides (MF)/Sézary syndrome (SS)
   10. Small cell lung cancer
   11. Soft tissue sarcoma
   12. Uterine sarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Central nervous system (CNS) cancer
Authorization of 12 months may be granted for treatment of CNS cancers.

B. Ewing sarcoma
Authorization of 12 months may be granted for treatment of Ewing sarcoma.

C. Neuroendocrine tumors
Authorization of 12 months may be granted for treatment of neuroendocrine tumors.

D. Extrapulmonary Poorly differentiated (high-grade) neuroendocrine carcinoma/large or small cell carcinoma
Authorization of 12 months may be granted for treatment of extrapulmonary poorly differentiated (high-grade) neuroendocrine carcinoma or large or small cell carcinoma.

E. Pheochromocytoma/paraganglioma
Authorization of 12 months may be granted for treatment of pheochromocytoma or paraganglioma.

F. Cutaneous Melanoma
Authorization of 12 months may be granted for treatment of cutaneous melanoma for metastatic or unresectable disease.

G. Uveal Melanoma
Authorization of 12 months may be granted for treatment of uveal melanoma for distant metastatic disease.

H. Mycosis fungoides (MF)/Sézary syndrome (SS)
Authorization of 12 months may be granted for treatment of MF or SS.

I. Small cell lung cancer (SCLC)
Authorization of 12 months may be granted for treatment of SCLC.

J. Soft tissue sarcoma (STS)
Authorization of 12 months may be granted for treatment of STS.

K. Uterine sarcoma
Authorization of 12 months may be granted for treatment of uterine sarcoma.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Temodar.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Central Nervous System Cancers
4. NCCN Guideline: Bone Cancer
5. NCCN Guideline: Neuroendocrine and Adrenal Tumors
6. NCCN Guideline: Melanoma: Cutaneous
7. NCCN Guideline: Melanoma: Uveal
8. NCCN Guideline: Primary Cutaneous Lymphomas
9. NCCN Guideline: Small Cell Lung Cancer
10. NCCN Guideline: Soft Tissue Sarcoma
11. NCCN Guideline: Uterine Neoplasms

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Temodar are covered in addition to central nervous system cancer, ewing sarcoma, neuroendocrine tumors, pheochromocytoma/paraganglioma, cutaneous and uveal melanoma, mycosis fungoides (MF)/Sézary syndrome (SS), small cell lung cancer, soft tissue sarcoma, and uterine sarcoma.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Temodar to treat central nervous system cancer, ewing sarcoma, neuroendocrine tumors, pheochromocytoma/paraganglioma, cutaneous and uveal melanoma, mycosis fungoides (MF)/Sézary syndrome (SS), small cell lung cancer, soft tissue sarcoma, and uterine sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Temodar [package insert]. Rahway, NJ: Merck & Co., Inc.; September 2023.
2. Temozolomide [package insert]. Durham, NC: Accord Healthcare, Inc.; January 2022.
3. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed November 2023.

TEPEZZA (teprotumumab-trbw)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Tepezza is indicated for the treatment of thyroid eye disease regardless of Thyroid Eye Disease activity or duration.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Supporting chart notes or medical record indicating moderate-to-severe disease as applicable to Section V.

III. EXCLUSIONS

Coverage will not be provided for repeat series of Tepezza infusions.

IV. CRITERIA FOR INITIAL APPROVAL

Thyroid eye disease (TED)
Authorization of 6 months may be granted for treatment of TED when all of the following criteria are met:
A. Member is 18 years of age or older
B. Member has moderate-to-severe (active and inactive) disease (see Appendix A)
C. Member will not exceed a one-time treatment course consisting of 8 infusions given once every 3 weeks (10mg/kg on first infusion, followed by 20mg/kg every 3 weeks for 7 additional infusions).

V. APPENDIX

Appendix A: Disease Severity Assessment
1. Mild disease, at least one of the following:
    a. Minor lid retraction (<2 mm)
    b. Mild soft-tissue involvement
    c. Exophthalmos <3 mm above normal for race and gender
    d. No or intermittent diplopia
    e. Corneal exposure responsive to lubricants
2. Moderate-to-severe disease, at least one of the following:
    a. Lid retraction ≥2 mm
    b. Moderate or severe soft-tissue involvement
    c. Exophthalmos ≥3 mm above normal for race and gender
    d. Inconstant or constant diplopia
3. Sight-threatening disease, at least one of the following:
    a. Dysthyroid optic neuropathy (DON)
    b. Corneal breakdown

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Tepezza.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis.
4. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tepezza are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCES

1. Tepezza [package insert]. Deerfield Lake, IL: Horizon Therapeutics USA Inc; July 2023.
2. Bartalena L, Kahaly L, Baldeschi L, et al. The 2021 European Thyroid Association/European Group on Graves' Orbitopathy guidelines for the management of Graves' orbitopathy. *Eur J Endocrinol. 2021*;185(4):G43-G67.
3. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343-1421.
4. Burch HB, Perros P, Bednarczuk T, Cooper DS, et al. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. *Thyroid*. 2022 Dec;32(12):1439-1470.
5. ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine. 2023 March 16 NCT04583735, *A Study Evaluating TEPEZZA® Treatment in Patients with Chronic (Inactive) Thyroid Eye Disease*; Accessed December 11, 2023.

TESTOPEL (testosterone pellet)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Males
Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.
a. Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome; or orchiectomy.
b. Hypogonadotropic hypogonadism (congenital or acquired) - gonadotropic LHRH deficiency, or pituitary - hypothalamic injury from tumors, trauma or radiation.

If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sex characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.
Safety and efficacy of Testopel (testosterone pellets) in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
c. Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An x-ray of the hand and wrist to determine bone age should be taken every 6 months to assess the effect of treatment on epiphyseal centers.

B. Compendial Use
1. Gender Dysphoria (also known as transgender or gender diverse (TGD) persons)
2. Delayed puberty

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Primary hypogonadism or Hypogonadotropic hypogonadism
Authorization of 12 months may be granted for treatment of primary or hypogonadotropic hypogonadism when all of the following criteria are met:
1. The requested drug is not being prescribed for "age-related hypogonadism" (also referred to as "late-onset hypogonadism")
2. The requested drug is being prescribed for primary or hypogonadotropic hypogonadism.
3. Before the start of testosterone therapy, the member has at least two confirmed low morning testosterone levels according to current practice guidelines or your standard lab reference values.

B. Gender dysphoria
Authorization of 12 months may be granted for treatment of gender dysphoria when all of the following criteria are met:
1. The member has a diagnosis of gender dysphoria.
2. The member has reached Tanner stage 2 of puberty or greater.

C. Delayed puberty
Authorization of 12 months may be granted when being prescribed for delayed puberty.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Testopel.
B. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Testopel.
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology
3. Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline
4. Standards of Care for the Health of Transgender and Gender Diverse People
5. Endocrine Treatment of Gender Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Testopel are covered in addition to gender dysphoria and delayed puberty.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Testopel to treat gender dysphoria and delayed puberty can be found in following compendial resources and guidelines: Micromedex DrugDex, Lexi-Drugs, Standards of Care for the Health of Transgender and Gender Diverse People, and Endocrine Treatment of Gender Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline.

VI. REFERENCES

1. Testopel (testosterone pellets) [package insert]. Malvern, PA: Endo Pharmaceuticals Inc.; August 2018.
2. Lexicomp Online, AHFS DI (Adult and Pediatric) Online, Hudson, Ohio: UpToDate, Inc.; 2023; Accessed November 2023.
3. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed November 2023.
4. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715-1744.
5. Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. Int J Transgend Health. 2022;23(S1):S1-S258.
6. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(11):3869-3903.
7. Health Care for Transgender and Gender Diverse Individuals. ACOG Committee Opinion No. 823. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2021;137:e75-88.
8. Palmetto GBA, LLC. Local Coverage Determination (LCD): Treatment of Males with Low Testosterone (L39086). Centers for Medicare & Medicaid Services, Inc. Updated on 04/25/2022 with effective date 05/05/2022. Accessed November 2023.

9. Palmetto GBA, LLC. Local Coverage Article (LCA): Billing and Coding: Treatment of Males with Low Testosterone (A58828). Centers for Medicare & Medicaid Services, Inc. Updated on 01/20/2022 with effective date 02/13/2022. Accessed November 2023.

TEZSPIRE (Tezepelumab-ekko)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Tezspire is indicated for add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

Limitations of use: Not for relief of acute bronchospasm or status asthmaticus.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration.
B. Continuation requests: Chart notes or medical record documentation supporting improvement in asthma control.

III. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted for treatment of severe asthma when both of the following criteria are met:
A. Member is 12 years of age or older.
B. Member has history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
    1. Inhaled corticosteroid
    2. Additional controller (i.e., long acting beta2-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline)
C. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, or Xolair).

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization of 12 months may be granted for when all of the following criteria are met:
A. Member is 12 years of age or older.
B. The member is currently receiving therapy with the requested medication.
C. The requested medication is being used to treat an indication enumerated in Section III.
D. The member is receiving benefit from therapy as defined by a reduction in the frequency and/or severity of symptoms and exacerbations.
E. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, or Xolair).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Tezspire.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2022 update.
4. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tezspire are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Tezspire to treat severe asthma can be found in the Global Initiative for Asthma (GINA) guidelines. For adults and adolescents 12 years of age and older, thymic stromal lymphopoietin (TSLP) blockers (anti-TSLP) can be a drug used when either medium dose maintenance inhaled corticosteroids with formoterol or medium to high dose maintenance inhaled corticosteroids with long-acting beta2-agonists are not controlling the patient's asthma.

VII. REFERENCES

1. Tezspire [package insert]. Thousand Oaks, CA: Amgen Inc.; February 2023
2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2022 update. Available at: https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf. Accessed March 1, 2023.
3. Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. *JAMA.* 2020;324(22): 2301-2317.

THYROGEN (thyrotropin alfa injection)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Thyrogen is indicated for use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy.
2. Thyrogen is indicated for use as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer.

B. Compendial Uses
1. Adjunct treatment for multinodular goiter
2. Adjunct treatment for thyroid cancer
3. Adjunct treatment for brain metastases

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Adjunctive diagnostic tool for well-differentiated thyroid cancer
Authorization of 1 month may be granted for use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing when ALL of the following criteria are met:
1. Member is receiving follow-up for well-differentiated thyroid cancer
2. Member has previously undergone a thyroidectomy

B. Adjunct treatment for thyroid remnant ablation
Authorization of 1 month may be granted as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants when ALL of the following criteria are met:
1. Member has received a near-total or total thyroidectomy for well-differentiated thyroid cancer
2. Member does not show evidence of distant metastatic thyroid cancer

C. Adjunct treatment for multinodular goiter
Authorization of 1 month may be granted when used for adjunct treatment prior to radioiodine treatment of large multinodular goiters.

D. Adjunct treatment for thyroid cancer
Authorization of 1 month may be granted when used as adjunct treatment for the stimulation of radioiodine uptake in the treatment of patients with differentiated thyroid carcinoma.

E. Adjunct treatment for brain metastases
Authorization of 1 month may be granted when used as adjunct treatment for the stimulation of radioiodine uptake for the treatment of brain metastases from thyroid cancer.

III. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Thyrogen.

2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Thyrogen and are covered in addition to the following:

1. Adjunct treatment for multinodular goiter
2. Adjunct treatment for thyroid cancer
3. Adjunct treatment for brain metastases

IV. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Thyrogen prior to radioiodine treatment of large multinodular goiters can be found in a prospective, controlled trial by Silva et al. The administration of recombinant human thyrotropin (rhTSH) prior to radioiodine therapy in patients with large, multinodular goiters has increased the efficacy of radioiodine uptake resulting in larger reductions in goiter volume as compared with radioiodine therapy alone. In a prospective, controlled trial (n=34), patients with very large, multinodular goiters (mean initial volume, 210 to 281 mL; range, 80 to 728 mL) with low or suppressed serum TSH levels received radioiodine treatment alone (mean iodine-131 dose, 3337 to 3552 megabecquerel) or were given a single intramuscular dose of rhTSH (0.45 mg) 24 hours prior to radioiodine treatment. All patients were also placed on a low-iodine diet. Serum thyroglobulin levels rose to significantly higher levels in patients pretreated with rhTSH as compared with patients who received radioiodine therapy only (p less than 0.05 at 24, 48, and 72 hours). Thyroid volume was significantly reduced in both treatment groups, however, a significantly greater mean individual reduction of thyroid volume was observed at 1 year in patients who received adjunctive rhTSH as compared with patients who received radioiodine therapy alone (57.8% vs 39.7%, respectively; p less than 0.05).

Limited data suggest effective use of recombinant human TSH to stimulate 131-iodine uptake in the treatment of patients with differentiated thyroid carcinoma. In one case report by Rudavsky et al, intramuscular administration of 0.9 mg daily for two days, followed by a large oral dose of 131-iodine (515 mCi), led to significant uptake in multiple metastatic lesions and clinical remission. With this treatment, it may be possible to continue thyroid suppression therapy and thereby avoid associated hypothyroid morbidity. The NCCN Guideline for thyroid carcinoma also supports using Thyrogen in elderly patients for whom prolonged hypothyroidism may be risky.

In another case report by Chiu et al, recombinant human thyrotropin safely stimulated radioiodine uptake for treatment of brain metastases from thyroid carcinoma. However, survival benefit was not obtained. Clinical studies are needed to further define the role of recombinant human TSH in treatment.

V. REFERENCES

1. Thyrogen [package insert]. Cambridge, MA: Genzyme Corporation; March 2020.
2. IBM Micromedex® DRUGDEX ® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com. (Accessed: July 25, 2023)
3. Silva MNC, Rubio IGS, Romao R, et al: Administration of a single dose of recombinant human thyrotropin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. Clin Endocrinol 2004; 60:300-308.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Thyroid Carcinoma. Version 3.2023. Accessed August 3, 2023. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
5. Rudavsky AZ & Freeman LM: Treatment of scan-negative, thyroglobulin-positive metastatic thyroid cancer using radioiodine 131-I and recombinant human thyroid stimulation hormone. J Clin Endocrinol Metabolism 1997; 82:11-14.
6. Chiu AC, Delpassand ES, & Sherman SI: Prognosis and treatment of brain metastases in thyroid carcinoma. J Clin Endocrinol Metab 1997; 82(11):3637-3642.

TIVDAK (tisotumab vedotin-tftv)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Tivdak is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Cervical Cancer
Authorization of 12 months may be granted for treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, as a single agent.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen, and
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Tivdak.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Cervical cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tivdak are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Tivdak [package insert]. Bothell, WA: Seagen Inc.; July 2023.

TORISEL (temsirolimus)
temsirolimus

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Advanced renal cell carcinoma (RCC)

B. Compendial Uses
1. Relapsed or stage IV renal cell carcinoma
2. Endometrial carcinoma
3. Soft tissue sarcoma subtypes:
   a. Perivascular epithelioid cell tumors (PEComa)
   b. Rhabdomyosarcoma
   c. Angiomyolipoma
   d. Lymphangioleiomyomatosis
5. Mantle cell lymphoma (MCL)
6. Uterine sarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Renal Cell Carcinoma
Authorization of 12 months may be granted as a single agent for treatment of advanced, relapsed, or stage IV renal cell carcinoma.

B. Endometrial Carcinoma
Authorization of 12 months may be granted as a single agent for subsequent treatment of recurrent endometrial carcinoma.

C. Soft Tissue Sarcoma
1. Authorization of 12 months may be granted for treatment of any of the following subtypes of soft tissue sarcoma as single agent therapy: locally advanced unresectable or metastatic perivascular epithelioid cell tumor (PEComa), recurrent angiomyolipoma, or recurrent lymphangioleiomyomatosis.
2. Authorization of 12 months may be granted for treatment of rhabdomyosarcoma in combination with cyclophosphamide and vinorelbine.

D. Mantle Cell Lymphoma
Authorization of 12 months may be granted for treatment of relapsed or refractory mantle cell lymphoma.

E. Uterine Sarcoma
Authorization of 12 months may be granted as a single agent for subsequent treatment of advanced, recurrent/metastatic, or inoperable PEComa.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Torisel
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Kidney Cancer
4. NCCN Guideline: Uterine Neoplasms
5. NCCN Guideline: Soft Tissue Sarcoma
6. NCCN Guideline: B-Cell Lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Torisel are covered in addition to relapsed or stage IV renal cell carcinoma, endometrial carcinoma, soft tissue sarcoma subtypes, mantle cell lymphoma (MCL), and uterine sarcoma.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Torisel to treat relapsed or stage IV renal cell carcinoma, endometrial carcinoma, soft tissue sarcoma subtypes, mantle cell lymphoma (MCL), and uterine sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Torisel [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; April 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed March 2024.
3. Clinical Pharmacology. Elsevier Inc. Available at: https://www.clinicalkey.com/pharmacology/. Accessed March 2024.
4. Hess G, Herbrecht R, Romaguerra J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2009;27:3822-29.

TREANDA (bendamustine)
BENDEKA (bendamustine)
BELRAPZO (bendamustine)
VIVIMUSTA (bendamustine)
bendamustine

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Chronic lymphocytic leukemia (CLL)
2. Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

B. Compendial Use
1. Classical Hodgkin lymphoma (CHL)
2. Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
3. Multiple myeloma (MM)
4. Small lymphocytic lymphoma (SLL)
5. B-cell lymphomas:
    i. Human immunodeficiency virus (HIV)-related B-cell lymphoma
    ii. Diffuse large B-cell lymphoma (DLBCL)
    iii. Follicular lymphoma (FL)
    iv. Marginal zone lymphoma
        a. Nodal marginal zone lymphoma
        b. Gastric mucosa associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone lymphoma of the stomach)
        c. Nongastric MALT lymphoma (nongastric extranodal marginal zone lymphoma)
        d. Splenic marginal zone lymphoma
    v. Mantle cell lymphoma (MCL)
    vi. Post-transplant lymphoproliferative disorders
    vii. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
    viii. High grade B-cell lymphoma
6. T-cell lymphomas:
    i. Adult T-cell leukemia/lymphoma (ATLL)
    ii. Hepatosplenic T-Cell lymphoma
    iii. Peripheral T-cell lymphoma (PTCL)
    iv. Breast implant associated anaplastic large cell lymphoma (ALCL)
7. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LL)/Bing-Neel syndrome
8. Small cell lung cancer
9. Metastatic breast cancer
10. Systemic light chain amyloidosis
11. Hematopoietic cell transplantation
12. Cold agglutinin disease

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. B-cell lymphoma

Authorization of 12 months may be granted for treatment of B-cell lymphoma with any of the following subtypes:

1. Follicular lymphoma
2. Diffuse large B-cell lymphoma (DLBCL) when all of the following criteria are met:
   i. The requested drug is used as subsequent therapy
   ii. The requested drug is used in combination with polatuzumab vedotin-piiq with or without rituximab
   iii. The member is not a candidate for transplant or the requested drug will be used as a bridging option until CAR T-cell product is available
3. Human immunodeficiency virus (HIV)-related B-cell lymphoma (HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma, plasmablastic lymphoma) when all of the following criteria are met:
   i. The requested drug is used as subsequent therapy
   ii. The requested drug is used in combination with polatuzumab vedotin-piiq with or without rituximab
   iii. The member is not a candidate for transplant or the requested drug will be used as a bridging option until CAR T-cell product is available
4. Marginal zone lymphoma
   i. Nodal marginal zone lymphoma when used in combination with rituximab or obinutuzumab
   ii. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone lymphoma of the stomach) when used in combination with rituximab or obinutuzumab
   iii. Nongastric MALT lymphoma (nongastric extranodal marginal zone lymphoma) when used in combination with rituximab or obinutuzumab
   iv. Splenic marginal zone lymphoma when used in combination with rituximab or obinutuzumab
5. Mantle cell lymphoma (MCL) when either of the following criteria are met:
   i. The requested drug is used in combination with rituximab, or
   ii. The requested drug as a component of RBAC500 (rituximab, bendamustine, and cytarabine).
6. Post-transplant lymphoproliferative disorders when all of the following criteria are met:
   i. The requested drug is used as subsequent therapy
   ii. The member is not a candidate for transplant or the requested drug will be used as a bridging option until CAR T-cell product is available
   iii. The requested drug will be used in combination with polatuzumab vedotin-piiq with or without rituximab
7. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma when all of the following criteria are met:
   i. The requested drug is used in combination with polatuzumab vedotin-piiq with or without rituximab.
   ii. The requested drug is used as subsequent therapy
   iii. The member is not a candidate for transplant.

8. High grade B-cell lymphoma when all of the following criteria are met:
   i. The requested drug is used as subsequent therapy
   ii. The requested drug will be used in combination with polatuzumab vedotin-piiq with or without rituximab

B. T-cell lymphoma

Authorization of 12 months may be granted for treatment of T-cell lymphoma with any of the following subtypes:

1. Adult T-cell leukemia/lymphoma (ATLL) when all of the following criteria are met:
   i. The requested drug is used as a single agent
   ii. The requested drug is used as subsequent therapy
2. Hepatosplenic T-Cell lymphoma when all of the following criteria are met:
   i. The requested drug is used as a single agent
   ii. The requested drug is used for refractory disease after 2 first-line therapy regimens
3. Peripheral T-cell lymphoma (PTCL) [including the following subtypes: anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral

T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma] when all of the following criteria are met:
   i. The requested drug is used as a single agent
   ii. The requested drug is used as palliative or subsequent therapy
4. Breast implant associated anaplastic large cell lymphoma (ALCL) when all of the following criteria are met:
   i. The requested drug is used as a single agent
   ii. The requested drug is used as subsequent therapy

C. Chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL)
Authorization of 12 months may be granted for treatment of CLL/SLL without chromosome 17p deletion or TP53 mutation

D. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LL)/Bing-Neel syndrome
Authorization of 12 months may be granted for treatment of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma or Bing-Neel syndrome when either of the following criteria are met:
1. The requested drug will be used in combination with rituximab, or
2. The requested will be used as a single agent

E. Multiple myeloma (MM)
Authorization of 12 months may be granted for treatment of MM when all of the following criteria are met:
1. The disease is relapsed or progressive and the member has tried more than 3 prior therapies, and
2. The requested drug will be used in any of the following regimens:
   i. In combination with lenalidomide and dexamethasone, or
   ii. In combination with bortezomib and dexamethasone, or
   iii. In combination with carfilzomib and dexamethasone, or
   iv. As a single agent

F. Classical Hodgkin lymphoma (cHL)
Authorization of 12 months may be granted for treatment of cHL when all of the following criteria are met:
1. The requested drug will be used as subsequent therapy or palliative therapy, and
2. The requested drug will be used in any of the following regimens:
   i. In combination with brentuximab vedotin, or
   ii. In combination with gemcitabine and vinorelbine, or
   iii. In combination with carboplatin and etoposide
   iv. As a single agent

G. Small cell lung cancer
Authorization of 12 months may be granted for the subsequent treatment of small cell lung cancer when used as a single agent.

H. Metastatic breast cancer
Authorization of 12 months may be granted for the treatment of metastatic breast cancer when used as a single agent or in combination with chemotherapy.

I. Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
Authorization of 12 months may be granted for the treatment of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) when all of the following criteria are met:
1. The requested drug will be used as subsequent therapy
2. The requested drug will be used in combination with rituximab

J. Systemic light chain amyloidosis
Authorization of 12 months may be granted for the treatment of systemic light chain amyloidosis when all of the following criteria are met:
1. The requested drug will be used in combination with dexamethasone
2. The requested drug will be used to treat relapsed or refractory disease

K. Hematopoietic Cell Transplantation

Authorization of 12 months may be granted for use in hematopoietic cell transplantation when all of the following criteria are met:
1. The requested drug will be used as conditioning for autologous transplant
2. The requested drug will be used in combination with etoposide, cytarabine and melphalan

L. Cold agglutinin disease
Authorization of 12 months may be granted for treatment of cold agglutinin disease when used in combination with rituximab.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested drug.
B. The requested drug is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
   i. No evidence of unacceptable toxicity while on the current regimen AND
   ii. No evidence of disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Treanda, Bendeka, Belrapzo, and Vivimusta.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN guideline: Waldenstrom macroglobulinemia/Lymphoplasmacytic lymphoma
4. NCCN guideline: Systemic light chain amyloidosis
5. NCCN guideline: Hodgkin lymphoma
6. NCCN guideline: Multiple myeloma
7. NCCN guideline: Small cell lung cancer
8. NCCN guideline: T-cell lymphomas
9. NCCN guideline: Pediatric Hodgkin lymphoma
10. NCCN guideline: Hematopoietic cell transplantation
11. NCCN guideline: B-cell lymphomas
12. NCCN guideline: Chronic lymphocytic leukemia/small lymphocytic lymphoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Treanda, Bendeka, Belrapzo and Vivimusta are covered in addition to the following:
1. Classical Hodgkin lymphoma (CHL)
2. Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
3. Multiple myeloma (MM)
4. Small lymphocytic lymphoma (SLL)
5. B-cell lymphomas:
   i. Human immunodeficiency virus (HIV)-related B-cell lymphoma
   ii. Diffuse large B-cell lymphoma (DLBCL)
   iii. Follicular lymphoma (FL)
   iv. Marginal zone lymphoma
      a. Nodal marginal zone lymphoma
      b. Gastric mucosa associated lymphoid tissue (MALT) lymphoma
      c. Nongastric MALT lymphoma
      d. Splenic marginal zone lymphoma
   v. Mantle cell lymphoma (MCL)

vi. Post-transplant lymphoproliferative disorders
vii. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
viii. High grade B-cell lymphoma

6. T-cell lymphomas:
   i. Adult T-cell leukemia/lymphoma (ATLL)
   ii. Hepatosplenic T-Cell lymphoma
   iii. Peripheral T-cell lymphoma (PTCL)
   iv. Breast implant associated anaplastic large cell lymphoma (ALCL)
7. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LL)
8. Small cell lung cancer
9. Metastatic breast cancer
10. Systemic light chain amyloidosis
11. Hematopoietic cell transplantation
12. Cold agglutinin disease

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the requested medication to treat the following indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

1. Classical Hodgkin lymphoma (CHL)
2. Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
3. Multiple myeloma (MM)
4. Small lymphocytic lymphoma (SLL)
5. B-cell lymphomas:
   i. Human immunodeficiency virus (HIV)-related B-cell lymphoma
   ii. Diffuse large B-cell lymphoma (DLBCL)
   iii. Follicular lymphoma (FL)
   iv. Marginal zone lymphoma
      a. Nodal marginal zone lymphoma
      b. Gastric mucosa associated lymphoid tissue (MALT) lymphoma
      c. Nongastric MALT lymphoma
      d. Splenic marginal zone lymphoma
      v. Mantle cell lymphoma (MCL)
   vi. Post-transplant lymphoproliferative disorders
   vii. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
   viii. High grade B-cell lymphoma
6. T-cell lymphomas:
   i. Adult T-cell leukemia/lymphoma (ATLL)
   ii. Hepatosplenic T-Cell lymphoma
   iii. Peripheral T-cell lymphoma (PTCL)
   iv. Breast implant associated anaplastic large cell lymphoma (ALCL)
7. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LL)
8. Small cell lung cancer
9. Metastatic breast cancer
10. Systemic light chain amyloidosis
11. Hematopoietic cell transplantation

Support for using the requested medication for metastatic breast cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). In a multinational, randomized, phase 3 trial, first-line treatment with bendamustine, methotrexate, and 5-fluorouracil significantly increased the median time to progression (8.2 months) compared with

cyclophosphamide, methotrexate, and 5-fluorouracil (6.7 months) in patients with metastatic breast cancer; although, overall response rates were not significantly different between the 2 treatment arms (confirmed response, 22.3% and 22.4%, respectively).

Support for using bendamustine to treat cold agglutinin disease can be found in the guidelines published by Jager et al. In patients with symptomatic, primary cold agglutinin disease, first-line treatment consists of rituximab alone, or rituximab plus bendamustine in fit patients. For second-line therapy, Rituximab plus bendamustine should be given if not previously used, or in patients who responded to it as first-line therapy and at least 2 years have passed since treatment.

VI. REFERENCES

1. Treanda [package insert]. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; October 2022.
2. Bendeka [package insert]. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; October 2021.
3. Belrapzo [package insert]. Woodcliff Lake, NJ; Eagle Pharmaceuticals, Inc; June 2022.
4. Vivimusta [package insert]. Princeton, NJ; Slayback Pharma LLC; December 2022.
5. Bendamustine [package insert]. Durham, NC; Accord Healthcare Inc; February 2018.
6. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 5, 2023.
7. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com Accessed April 8, 2023.
8. Jager U, Barcellini W, Broome CM, et al: Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. Blood Rev 2020; 41:100648-.

TRELSTAR (triptorelin pamoate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Trelstar is indicated for the palliative treatment of advanced prostate cancer

B. Compendial Uses
1. Prostate cancer
2. Gender dysphoria
3. Preservation of ovarian function
4. Breast cancer – ovarian suppression
5. Endometrial hyperplasia
6. Endometriosis
7. Fibrocystic breast changes
8. Uterine leiomyoma
9. Carcinoma of the pancreas
10. Ovarian carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Hormone receptor status testing results (where applicable).

III. CRITERIA FOR INITIAL APPROVAL

A. Prostate cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

B. Gender dysphoria
1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member has reached Tanner stage 2 of puberty or greater.
2. Authorization of 12 months may be granted for gender transition when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member will receive the requested medication concomitantly with gender-affirming hormones.

C. Preservation of ovarian function
Authorization of 3 months may be granted for preservation of ovarian function when the member is premenopausal and undergoing chemotherapy.

D. Breast cancer – ovarian suppression

Authorization of 12 months may be granted for ovarian suppression in hormone-receptor positive breast cancer when all of the following criteria are met:
1. The member is premenopausal.
2. There is a higher risk for recurrence (e.g., young age, high-grade tumor, lymph-node involvement).
3. The requested medication will be used in combination with endocrine therapy.

E. Endometrial hyperplasia
Authorization of 12 months may be granted for treatment of non-atypical endometrial hyperplasia

F. Endometriosis
Authorization of up to 6 months total therapy may be granted for treatment of endometriosis.

G. Fibrocystic breast changes
Authorization of 3 months may be granted for treatment of benign fibrocystic mastopathy when either of the following criteria is met:
1. The requested medication will be used as a single agent.
2. The requested medication will be used in combination with tamoxifen or cyproterone.

H. Uterine Leiomyoma
Authorization of up to 6 months total therapy may be granted for treatment of uterine fibroids.

I. Adenocarcinoma of pancreas
Authorization of 12 months may be granted for treatment of adenocarcinoma of the pancreas.

J. Ovarian carcinoma
Authorization of 12 months may be granted for treatment of ovarian carcinoma.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat one of the following indications enumerated in Section III:
      a. Adenocarcinoma of pancreas
      b. Ovarian carcinoma
      c. Gender dysphoria
      d. Endometrial hyperplasia
      e. Fibrocystic breast changes
   3. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

B. Authorization of 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used for prostate cancer.
   3. The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced an unacceptable toxicity.

C. Authorization of 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used for ovarian suppression in hormone receptor positive breast cancer.
   3. The member was premenopausal at diagnosis and still undergoing treatment with endocrine therapy.
   4. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

D. Authorization for 3 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.

2. The requested medication is being used for preservation of ovarian function.
3. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

E. All other indications
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Trelstar.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Uterine neoplasms
4. NCCN Guideline: Prostate cancer
5. Fertility preservation in patients with cancer: ASCO clinical practice guideline update.
6. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression.
7. ESHRE guideline: endometriosis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Trelstar are covered in addition to the following:
1. Prostate cancer
2. Gender dysphoria
3. Preservation of ovarian function
4. Breast cancer – ovarian suppression
5. Endometrial hyperplasia
6. Endometriosis
7. Fibrocystic breast changes
8. Uterine leiomyoma
9. Carcinoma of the pancreas
10. Ovarian carcinoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Trelstar to treat prostate cancer in settings not covered in the prescribing information can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Trelstar for gender dysphoria can be found in the Endocrine Society Clinical Practice guideline for endocrine treatment of gender-dysphoric/gender-incongruent persons. The guidelines support GnRH agonist use in both transgender males and transgender females. Specific products are not listed; therefore, coverage is applied to the entire class of GnRH agonists.
Support for using Trelstar for gender dysphoria can also be found in the World Professional Association for Transgender Health (WPATH). According to the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, prescribing GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (defined as past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy. PATH also recommends beginning

pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

WPATH recommends health care professionals prescribe progestins or a GnRH agonist for eligible transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.
WPATH also recommends health care professionals prescribe testosterone-lowering medications (including GnRH agonists) for eligible transgender and gender diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.

Support for using Trelstar for preservation of ovarian function can be found in the ASCO Clinical Practice Guidelines for fertility preservation in patients with cancer. The guideline indicates gonadotropin-releasing hormone receptor agonist therapy may be offered to young women, especially those with breast cancer, in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency when proven fertility preservation methods (i.e., oocyte, embryo, or ovarian tissue cryopreservation) are not feasible. Gonadotropin-releasing hormone receptor agonists should not be used in place of proven fertility preservation methods.

Support for using Trelstar for ovarian suppression in patients with breast cancer can be found in the National Comprehensive Cancer Network's guideline for breast cancer. The NCCN Guideline for breast cancer supports the use of gonadotropin releasing hormone agonists during adjuvant chemotherapy in premenopausal patients with breast tumors (regardless of hormone receptor status). The use of gonadotropin releasing hormone agonists may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Smaller historical experiences in patients with estrogen receptor-positive disease have reported conflicting results with regard to the protective effect of gonadotropin releasing hormone agonist therapy on fertility.
Additionally, support for using Trelstar for ovarian suppression in combination with endocrine therapy can be found in a study by Francis et al of 3066 premenopausal women with early-stage hormone receptor-positive breast cancer (SOFT study). Patients were randomized to receive 5 years of treatment with tamoxifen 20 mg daily, tamoxifen 20 mg daily and ovarian suppression, or exemestane 25 mg daily and ovarian suppression. Ovarian suppression could be achieved with triptorelin 3.75 mg administered by IM injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation. Approximately one-half (53%) of patients enrolled in the study had received prior adjuvant chemotherapy. The primary analysis involved comparison of tamoxifen and ovarian suppression with tamoxifen alone. At a median follow-up of 8 years, disease-free survival and overall survival were prolonged, without a reduction in distant recurrences, in women receiving tamoxifen and ovarian suppression compared with those receiving tamoxifen alone; a disease-free survival benefit and a reduction in distant recurrences were observed, without an overall survival benefit, in women receiving exemestane and ovarian suppression compared with those receiving tamoxifen alone. Subgroup analysis in the SOFT study suggested that the relative clinical benefits of the 3 treatments generally were similar regardless of prior use of adjuvant chemotherapy; however, no difference in disease-free survival was observed with the addition of ovarian suppression to tamoxifen therapy in patients at lower risk of breast cancer recurrence (i.e., older age, node-negative disease, low-grade tumor, smaller tumor size) who had not required prior adjuvant chemotherapy. The absolute benefit of combined endocrine and ovarian suppression therapy was greater in higher-risk patients who had received adjuvant chemotherapy.
Based on current evidence, use of endocrine therapy (i.e., anastrozole, exemestane, letrozole, tamoxifen) in combination with ovarian suppression as adjuvant therapy may be considered a reasonable choice (accepted) in premenopausal women with early-stage hormone receptor-positive breast cancer at higher risk of disease recurrence (i.e., younger age, larger or high-grade tumor, increased risk of lymph node involvement) and those who received prior adjuvant chemotherapy. ASCO states that the duration of adjuvant GnRH agonist therapy should not exceed 5 years, since the toxicity of long-term (e.g., beyond 5 years) use of GnRH agonist-induced ovarian suppression has not been determined and comparative data for alternative treatment durations are lacking.

Support for using Trelstar to treat endometrial hyperplasia can be found in a study by Grimbizis et al. Long-acting triptorelin treatment returned hyperplastic endometrium to normal in most women with non-atypical hyperplasia but was ineffective in women with atypical hyperplasia. Triptorelin 3.75 mg in the form of sustained-release microcapsules was administered once every 4 weeks, on the first or second day of the menstrual cycle, for 6 months to women with simple (adenocystic) hyperplasia (n=39), complex (adenomatous) hyperplasia (n=14), or atypical complex (atypical adenomatous) hyperplasia (n=3). Among

women with non-atypical forms (simple and complex), 85% responded with a return to normal endometrium, 57% functional and 29% atrophic. None of the women with atypical hyperplasia responded with a return to normal tissue. Sixty-eight percent of women experienced hot flushes, the most common side effect; 37.5% developed vaginal atrophy.

Support for using Trelstar to treat endometriosis can be found in the European Society of Human Reproduction and Endocrinology (ESHRE) endometriosis guidelines. In adults, GnRH agonists can be given to reduce endometriosis pain; evidence is limited for dosage or duration of therapy. Combined hormonal "add back" therapy should be considered concomitantly with GnRH agonists to prevent hypoestrogenic symptoms and bone loss. GnRH agonists should be given second line (e.g., if progestins or hormonal contraceptives are not effective) due to their side effect profile. In adolescents, GnRH agonists can be prescribed to adolescents for the treatment of pain associated with laparoscopically confirmed endometriosis in cases where hormonal contraceptives or progestins have failed. Duration of therapy is up to 1 year since GnRH agonists are safe and effective in combination with add back therapy. GnRH agonist therapy in adolescents and young women should only be considered after careful consideration of potential long-term health risks and side effects.

Support for using Trelstar to treat fibrocystic breast changes can be found in a study by Monsonego et al. Intramuscular triptorelin (microsphere formulation) 3.75 mg every 28 days for 3 months has been effective in treating benign fibrocystic mastopathy. The additional use of tamoxifen (estrogen receptor-positive patients) or cyproterone (progesterone receptor-positive) with triptorelin for 3 further months has enabled complete responses to occur in about one-third of women achieving only partial response during 3 months of triptorelin monotherapy. Complete remission has been reported in over 50% of patients receiving triptorelin alone or combined with tamoxifen or cyproterone.

Support for using Trelstar to treat uterine fibroids can be found in a study by Vercellini et al. Treatment of women with triptorelin before hysterectomy for uterine leiomyomas increased the proportion that could be accomplished by a vaginal, rather than abdominal, procedure. One hundred twenty-three premenopausal women with a clinically assessed uterine volume of 12 to 16 gestational weeks were randomly assigned to receive immediate surgery or to be treated with 3 intramuscular depot injections of triptorelin 3.75 mg, separated by 28 days, before surgery. The percentage of operations that could be performed vaginally in the immediate surgery group was 16%. Of those women assigned to pre-treatment, the starting assessment was that 12% were suited to the vaginal procedure. After treatment with triptorelin, 53% were accomplished with the vaginal procedure (p less than 0.0001 between groups). This 37% reduction in risk for an abdominal surgery indicates that 3 women would need to be treated with triptorelin to avoid one abdominal surgery.
A study published by Broekmans and colleagues of 27 premenopausal women with uterine fibroids, the benefits of initial high-dose treatment for 8 weeks were prolonged by low-dose treatment for 18 additional weeks. In the initial phase of the study, all women began daily subcutaneous self-administration of aqueous triptorelin solutions. The doses were 500 mcg daily for the first week followed by a daily dose of 100 mcg for 7 weeks. The patients were then randomized to one of 3 groups using 5, 20, or 100 mcg daily for 18 weeks. After the first 8 weeks, the median uterine volume was reduced to 67.1% of the baseline volume (p=0.001) and after the full 26-week course, median uterine volume was reduced to 57.8% (p=0.001). The extent of additional decrease after 8 weeks appeared to be dose-dependent although no differences in overall volume reduction were found at 26 weeks. No significant change in median bone mineral density was observed.

Support for using Trelstar to treat adenocarcinoma of pancreas can be found in a published case report. A case report published by Gonzelez-Barcena and colleagues evaluated the use of GnRH agonists in 17 patients with unresectable and biopsy-proven adenocarcinoma of the pancreas (stage IV). Nine patients were male and 8 female, and the median age at diagnosis was 60 years. The majority of patients underwent a gastro-intestinal and biliary bypass. The therapy with D-Trp-6-LH-RH was started 3-31 days after bypass surgery. The analog was given at the dose of 1 mg/day subcutaneously for the first 7 days. Subsequently, the dose was reduced to 100 micrograms/day. One month after the start of the therapy the gonadotropin levels were in subnormal range. This therapy led to clinical improvement, better quality of life and an increase in survival time. The median survival time for all the groups was 7.2 months (men 7.4 months and women 6.9 months). LH-RH agonists appear to decrease pancreatic cancer growth by eliminating the stimulatory effect of sex steroids, and by direct effects on tumors. Further improvement in the clinical response in patients with inoperable pancreatic carcinoma might be possibly obtained by the combination of LH--RH agonists with modern somatostatin analogs.

Support for using Trelstar to treat ovarian carcinoma can be found in a study by Duffaud and colleagues. Triptorelin had only minor efficacy when used to treat ovarian carcinoma in women who had been pretreated with platinum-containing chemotherapy. Pretreated women (n=69) received intramuscular injections of microencapsulated triptorelin 3.75 mg on days 1, 8 and 28, and then every 4 weeks until disease progression. There were no objective responses. Only 11 of 69 (16%) of the patients achieved stable disease, with a median duration of 6 months. Median overall survival time for those with disease stabilization was 17 months. The drug was well tolerated, with only mild hot flushes and headaches reported in a few patients. Additionally, a partial response to triptorelin was observed in 6 of 41 advanced ovarian carcinoma patients (15%) who had relapsed after conventional therapy in one trial. Remission persisted for up to 18 months, and mean survival time was 10 months. Stable disease (6 to 12 months) was observed in an additional 5 patients (12%). Responses to triptorelin appeared to be better in older patients in this study but were not correlated with histological grade or subtype of cancer (Parmar et al).

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Remodulin (treprostinil injection)
treprostinil injection

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

1. Pulmonary Arterial Hypertension
   Indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH, PAH associated with congenital systemic-to-pulmonary shunts, or PAH associated with connective tissue diseases.
2. Pulmonary Arterial Hypertension in Patients Requiring Transition from Epoprostenol
   Indicated in patients with PAH, requiring transition from epoprostenol, to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

Compendial Use

Severe peripheral ischemia

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Pulmonary Arterial Hypertension (PAH)

Indefinite authorization may be granted for treatment of pulmonary hypertension when ALL of the following criteria are met:

1. The pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left-sided atrial or ventricular disease, left-sided valvular heart disease, etc.) or disorders of the respiratory system (e.g., chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea, or other sleep disordered breathing, alveolar hypoventilation disorders, etc.).
2. The member has primary pulmonary hypertension or pulmonary hypertension, which is secondary to one of the following conditions: connective tissue disease, thromboembolic disease of pulmonary arteries, human immunodeficiency virus (HIV) infection, cirrhosis, diet drugs, congenital left to right shunts, etc. If these conditions are present, all of the following criteria must be met:
   i. The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition.
   ii. The mean pulmonary artery pressure is greater than 25 mmHg at rest or greater than 30 mmHg with exertion.
   iii. The member has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope).
   iv. Treatment with oral calcium channel blocking agents has been tried and failed or has been considered and ruled out.

B. Severe Peripheral Ischemia

Authorization of 12 months may be granted for treatment of severe peripheral ischemia.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit.

A. Pulmonary Arterial Hypertension (PAH)
Authorization for members who are requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. Severe Peripheral Ischemia
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat severe peripheral ischemia.
3. The member is receiving benefit from therapy. Benefit is defined as either:
   a. Disease stability
   b. Disease improvement

IV. APPENDIX

WHO Classification of Pulmonary Hypertension

1 PAH

1.1 Idiopathic (PAH)
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4. PAH associated with:
- 1.4.1 Connective tissue diseases
- 1.4.2 HIV infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart diseases
- 1.4.5 Schistosomiasis

1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease

2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders

4 PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
- 4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
- 4.2.2 Other malignant tumors
  - Renal carcinoma
  - Uterine carcinoma
  - Germ cell tumours of the testis
  - Other tumours
- 4.2.3 Non-malignant tumours
  - Uterine leiomyoma
- 4.2.4 Arteritis without connective tissue disease
- 4.2.5 Congenital pulmonary artery stenosis

4.2.6 Parasites
Hydatidosis

5 PH with unclear and/or multifactorial mechanisms

5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders
5.2 Systemic and metabolic disorders: Pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis
5.3 Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis
5.4 Complex congenital heart disease

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Remodulin and generic treprostinil.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. External Infusion Pumps Local Coverage Determination (L33794)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Remodulin and generic treprostinil are covered in addition to severe peripheral ischemia.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information and the external infusion pump Local Coverage Determination (L33794).

Support for using Remodulin or generic treprostinil to treat severe peripheral ischemia can be found in two small studies. Berman et al (2006) conducted an open-label study of 10 patients with at least 1 ischemic wound received treprostinil via an ambulatory subcutaneous infusion pump. The mean worst ischemic rest pain score decreased from baseline to week 12 by 62% and the mean average ischemic rest pain score decreased from baseline to week 12 by 57%. Three patients with small wounds (0.2 to 2 cm^2) had complete wound healing and no new wounds developed in any patient during the study period. Within 2 months following the end of the study, 3 patients had below the knee amputations as a result of wound progression. Additionally, Moher and colleagues conducted a sequential dose-escalation trial where 8 patients received an initial infusion rate of treprostinil 10 nanograms/kg/min followed by doubling of the infusion rate every 60 minutes until dose-limiting side effects (i.e., severe flushing, headache, nausea, or diarrhea) occurred. The maximum tolerated dose was determined to be 10 to 20 nanograms/kg/min. Blood flow in the common femoral artery was increased by 35% over baseline at the end of the maximum dosage, 29% over baseline at the end of the maintenance dosage, and 28% over baseline at the end of the washout phase.

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TRETTEN (coagulation Factor XIII A-subunit [recombinant])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Tretten is indicated in patients with congenital factor XIII A-subunit deficiency for routine prophylaxis for bleeding.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Congenital Factor XIII A-Subunit Deficiency
Authorization of 12 months may be granted for prophylactic treatment of congenital factor XIII A-subunit deficiency.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. Tretten is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Tretten.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tretten are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

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TRIPTODUR (triptorelin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Triptodur is indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty (CPP).

B. Compendial Use
1. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
2. Preservation of ovarian function
3. Prevention of recurrent menstrual related attacks in acute porphyria

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

A. The following documentation must be available, upon request, for all submissions:
1. For central precocious puberty, laboratory report or medical record of a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay.

III. CRITERIA FOR INITIAL APPROVAL

A. Central precocious puberty (CPP)
1. Authorization of 12 months may be granted for treatment of CPP in a female member when all of the following criteria are met:
   i. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI]).
   ii. The diagnosis of CPP has been confirmed by a pubertal response to a gonadotropin releasing hormone (GnRH) agonist test or a pubertal level of a third-generation luteinizing hormone (LH) assay.
   iii. The assessment of bone age versus chronological age supports the diagnosis of CPP.
   iv. The member was less than 8 years of age at the onset of secondary sexual characteristics.
2. Authorization of 12 months may be granted for treatment of CPP in a male member when all of the following criteria are met:
   i. Intracranial tumor has been evaluated by appropriate lab tests and diagnostic imaging (e.g., CT scan, MRI).
   ii. The diagnosis of CPP has been confirmed by a pubertal response to a GnRH agonist test or a pubertal level of a third generation LH assay.
   iii. The assessment of bone age versus chronological age supports the diagnosis of CPP.
   iv. The member was less than 9 years of age at the onset of secondary sexual characteristics.

B. Gender dysphoria
1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.

b. The member has reached Tanner stage 2 of puberty or greater.

2. Authorization of 12 months may be granted for gender transition when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member will receive the requested medication concomitantly with gender-affirming hormones.

C. Preservation of ovarian function

Authorization of 3 months may be granted for preservation of ovarian function when the member is premenopausal and undergoing chemotherapy.

D. Prevention of recurrent menstrual related attacks in acute porphyria

Authorization of 12 months may be granted for prevention of recurrent menstrual related attacks in members with acute porphyria.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.
B. Triptodur is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Triptodur.
2. The available compendium
   a. Micromedex DrugDex
   b. American Hospital Formulary Service- Drug Information (AHFS-DI)
   c. Lexi-Drugs
   d. Clinical Pharmacology
3. Standards of Care for the Health of Transgender and Gender Diverse People
4. Endocrine Treatment of Gender Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline.
5. ACOG Health Care for Transgender and Gender Diverse Individuals
6. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis
7. Best practice guidelines on clinical management of acute attacks of porphyria and their complications.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Triptodur are covered in addition to gender dysphoria.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Triptodur to treat gender dysphoria can be found in following compendial resources and guidelines: Micromedex DrugDex, Lexi-Drugs, Standards of Care for the Health of Transgender and Gender Diverse People, ACOG Health Care for Transgender and Gender Diverse Individuals, and Endocrine Treatment of Gender Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline.

Support for using Triptodur for preservation of ovarian function and prevention of recurrent menstrual related attacks in acute porphyria can be found in following compendial resources and guidelines: Micromedex DrugDex, Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis, and best practice guidelines on clinical management of acute attacks of porphyria and their complications.

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TRODELVY (sacituzumab govitecan-hziy)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
   2. Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine based therapy and at least two additional systemic therapies in the metastatic setting.
   3. Trodelvy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.

B. Compendial Uses
   1. Breast cancer
   2. Urothelial carcinoma
      i. Bladder cancer
      ii. Primary carcinoma of the urethra
      iii. Upper genitourinary tract tumors
      iv. Urothelial carcinoma of the prostate

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions where applicable:
Test results confirming status of the following receptors:
A. Human epidermal growth factor receptor 2 (HER2)
B. Estrogen
C. Progesterone

III. CRITERIA FOR INITIAL APPROVAL

A. Breast cancer
Authorization of 12 months may be granted as a single agent for treatment of breast cancer when either of the following criteria are met:
   1. The disease is recurrent, unresectable, metastatic, or the member had no response to preoperative systemic therapy and all of the following criteria are met:
      i. The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for all of the following receptors:
         a. Human epidermal growth factor receptor 2 (HER2)
         b. Estrogen
         c. Progesterone
      ii. The member has received at least two prior therapies, with at least one line for metastatic disease.

2. The disease is recurrent unresectable or metastatic or the member had no response to preoperative systemic therapy, and all of the following criteria are met:
    i. The cancer cells are hormone receptor positive and human epidermal growth factor receptor 2 (HER2)-negative.
    ii. The member has received prior treatment including all of the following:
        a. Endocrine therapy (e.g., anastrozole, letrozole, fulvestrant)
        b. A CDK4/6 inhibitor (e.g., abemaciclib, palbociclib, ribociclib)
        c. At least two lines of chemotherapy (including a taxane)
    iii. Member is not a candidate for fam-trastuzumab deruxtecan-nxki (Enhertu).

B. Urothelial Carcinoma – Bladder Cancer
Authorization of 12 months may be granted as a single agent for subsequent treatment of locally advanced, recurrent, persistent, or metastatic bladder cancer in members who have received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.

C. Urothelial Carcinoma – Primary Carcinoma of the Urethra
Authorization of 12 months may be granted as a single agent for subsequent treatment of locally advanced, recurrent or metastatic primary carcinoma of the urethra in members who have received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.

D. Urothelial Carcinoma – Upper Genitourinary Tract Tumors or Urothelial Carcinoma of the Prostate
Authorization of 12 months may be granted as a single agent for subsequent treatment of locally advanced or metastatic upper genitourinary tract tumors or urothelial carcinoma (UC) of the prostate in members who have received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met.
A. The member is currently receiving therapy with Trodelvy
B. Trodelvy is being used to treat an indication enumerated in Section III
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Trodelvy.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Breast cancer
4. NCCN Guideline: Bladder cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Trodelvy are covered in addition to the following:
    1. Breast cancer

2. Urothelial carcinoma
i. Bladder cancer
ii. Primary carcinoma of the urethra
iii. Upper genitourinary tract tumors
iv. Urothelial carcinoma of the prostate

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Trodelvy to treat breast cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Trodelvy to treat urothelial carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Trodelvy [package insert]. Foster City, CA: Gilead Sciences, Inc; February 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed December 4, 2023.

TROGARZO (ibalizumab-uiyk)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Trogarzo, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

A. The following documentation must be available, upon request, for all submissions:
   1. Medical record documentation (i.e., chart notes) confirming the diagnosis and treatment history.

III. CRITERIA FOR INITIAL APPROVAL

Human Immunodeficiency Virus Type 1 (HIV-1)
Authorization of 6 months may be granted to members for treatment of human immunodeficiency virus type 1 (HIV-1) when all the following are met:
1. The requested medication is being used in combination with other antiretroviral(s)
2. The member is heavily treatment-experienced
3. The member has multi-drug resistant HIV-1
4. The member is failing their current antiretroviral regimen

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Trogarzo
B. The requested medication is being used in combination with other antiretroviral(s)
C. The member has experienced disease stabilization or improvement in viral load while on therapy with Trogarzo
D. The member has no evidence of unacceptable toxicity (e.g. immune reconstitution inflammatory syndrome [IRIS]) while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Trogarzo
2. The available compendium
   a. Micromedex DrugDex
   b. American Hospital Formulary Service- Drug Information (AHFS-DI)
   c. Lexi-Drugs

d. Clinical Pharmacology
3. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Trogarzo are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Trogarzo [package insert]. Montreal, Quebec Canada; Thera technologies, Inc., October 2022. Accessed November 2023.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Last updated 3/23/2023. Accessed November 2023.

TYSABRI (natalizumab)
TYRUKO (natalizumab-sztn)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. As monotherapy treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
B. For inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α.

Important Limitations:
In CD, Tysabri and Tyruko should not be used in combination with immunosuppressants or inhibitors of TNF-α.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

Crohn's disease (CD):

A. Initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried, including response to therapy.
B. Continuation requests: Chart notes or medical record documentation supporting positive clinical response to therapy or remission.

III. CRITERIA FOR INITIAL APPROVAL

A. Relapsing forms of multiple sclerosis
Authorization of 12 months may be granted to members who have been diagnosed with a relapsing form of multiple sclerosis (including relapsing-remitting and secondary progressive disease for those who continue to experience relapse) and who have been tested for anti-JCV antibodies.

B. Clinically isolated syndrome
Authorization of 12 months may be granted to members for the treatment of clinically isolated syndrome of multiple sclerosis and who have been tested for anti-JCV antibodies.

C. Crohn's Disease (CD)
Authorization of 12 months may be granted to adult members who have received any other biologic indicated for the treatment of moderately to severely active Crohn's disease and who have been tested for anti-JCV antibodies.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Relapsing forms of multiple sclerosis and clinically isolated syndrome

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy.

B. Crohn's disease

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy. Benefit is defined as one of the following:
    i. Member has achieved or maintained remission.
    ii. Member has achieved or maintained a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in any of the following from baseline:
        a. Abdominal pain or tenderness
        b. Diarrhea
        c. Body weight
        d. Abdominal mass
        e. Hematocrit
        f. Appearance of the mucosa on endoscopy, computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound
        g. Improvement on a disease activity scoring tool (e.g., Crohn's Disease Activity Index [CDAI] score

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Tysabri and Tyruko.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. ACG Clinical Guideline: Management of Crohn's disease in adults
4. An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tysabri and Tyruko are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Tysabri [package insert]. Cambridge, MA: Biogen Inc; April 2023.
2. Tyruko [package insert]. Princeton, NJ: Sandoz Inc; August 2023.
3. Talley NJ, Abreu MT, Achkar J, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(Suppl 1):S2-S25.
4. Lichtenstein GR, Loftus Jr EV, Isaacs KI, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018;113:481-517.

TZIELD (teplizumab-mzwv)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Tzield is indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 type 1 diabetes.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Presence of two or more pancreatic islet cell autoantibodies within the past 6 months
B. Abnormal oral glucose tolerance test (OGTT) results within the past 2 months

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with an endocrinologist.

IV. CRITERIA FOR INITIAL APPROVAL

Delay of Stage 3 Type 1 Diabetes
Authorization of 1 month may be granted for members with Stage 2 type 1 diabetes to delay the onset of Stage 3 type 1 diabetes when all of the following criteria are met:
A. Member is 8 years of age and older
B. Member has two or more of the following pancreatic islet cell autoantibodies detected in two samples obtained within the past 6 months:
    1. Glutamic acid decarboxylase 65 (GAD) autoantibodies
    2. Insulin autoantibody (IAA)
    3. Insulinoma-associated antigen 2 autoantibody (IA-2A)
    4. Zinc transporter 8 autoantibody (ZnT8A)
    5. Islet cell autoantibody (ICA)
C. Member has an abnormal oral glucose tolerance test (OGTT) confirming dysglycemia within the past 2 months when any of the following are met:
    1. Fasting blood glucose level of 110 to 125 mg/dL (6.1 to 6.9 mmol/L)
    2. 2-hour postprandial plasma glucose level of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L)
    3. Intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter (11.1 mmol/L) on two occasions
D. Member does not have symptoms associated with type 1 diabetes (e.g., increased urination, excessive thirst, weight loss)
E. Member will not exceed a one-time 14-day treatment course consisting of the following dosing schedule:
    1. Day 1: 65 mcg/m^2
    2. Day 2: 125 mcg/m^2
    3. Day 3: 250 mcg/m^2

4. Day 4: 500 mcg/m^2
5. Days 5 through 14: 1,030 mcg/m^2

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Tzield.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tzield are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Tzield [package insert]. Red Bank, NJ: Provention Bio, Inc.; November 2022.
2. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med 2019; 381:603-613. https://www.nejm.org/doi/full/10.1056/nejmoa1902226.

ULTOMIRIS (ravulizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. Treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).
B. Treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).
C. Ultomiris is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

Limitations of Use:
Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. For initial requests:
   1. Paroxysmal nocturnal hemoglobinuria: flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency
   2. Generalized myasthenia gravis: anti-acetylcholine receptor (AchR) antibody positive, clinical classification of myasthenia gravis score, MG activities of daily living score
B. For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Paroxysmal Nocturnal Hemoglobinuria (PNH)
Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:
1. The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) as demonstrated by either of the following:
   i. At least 5% PNH cells
   ii. At least 51% of GPI-AP deficient poly-morphonuclear cells
2. Flow cytometry is used to demonstrate GPI-APs deficiency

B. Atypical hemolytic uremic syndrome (aHUS)
Authorization of 6 months may be granted for treatment of atypical hemolytic uremic syndrome (aHUS) that is not caused by Shiga toxin.

C. Generalized myasthenia gravis (gMG)
Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:
1. Anti-acetylcholine receptor (AchR) antibody positive
2. Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV
3. MG activities of daily living (MG-ADL) total score ≥6

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Paroxysmal Nocturnal Hemoglobinuria (PNH)
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Ultomiris
2. The member is receiving benefit from therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels)

B. Atypical hemolytic uremic syndrome (aHUS)
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Ultomiris
2. The member is receiving benefit from therapy (e.g., normalization of lactate dehydrogenase [LDH] levels, platelet counts)

C. Generalized myasthenia gravis (gMG)
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Ultomiris
2. The member is receiving benefit from therapy (e.g., improvement in MG-ADL score, changes compared to baseline in Quantitative Myasthenia Gravis (QMG) total score)

V. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Ultomiris.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy.
4. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry.
5. International consensus guidance for management of myasthenia gravis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ultomiris are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using percentage of PNH cells or percentage of GPI-AP deficiency poly-morphonuclear cells can be found in the guidelines for diagnosis of PNH (Borowitz et al and Preis et al). Flow cytometry is the gold standard for assessing the percentage of GPI-AP deficient poly-morphonuclear cells. Classic PNH is defined as greater than 50% of GPI-AP deficient PMNs. It is also possible to diagnose PNH by assessing the

percentage of PNH cells. Most clinical trials for the complement inhibitors required at least 10% PNH cells, but the trials associated with Ultomiris only required 5% PNH cells. Therefore, the baseline requirement for all complement inhibitor programs will be at least 5%.

VIII. REFERENCES

1. Ultomiris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; April 2022.
2. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. Hematology. 2011; 21-29.
3. Lee JW, Sicre de Fontbrune F, Wong LL, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: The 301 study. Blood. 2019;133(6):530-539. doi:10.1182/blood-2018-09-876136.
4. Borowitz MJ, Craig F, DiGiuseppe JA, et al. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry. Cytometry B Clin Cytom. 2010: 78: 211-230.
5. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.
6. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2021; 96 (3) 114-122.
7. Tuan Vu, Andreas Meisel, Renato Mantegazza, et al. Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. NEJM Evid 2022; 1 (5)
8. Dezern AE, Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018 Jan;94(1):16-22.

UPLIZNA (inebilizumab-cdon)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Uplizna is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests: Immunoassay used to confirm anti-aquaporin-4 (AQP4) antibody is present.
B. For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

Neuromyelitis optica spectrum disorder (NMOSD)
Authorization of 12 months may be granted for treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:
A. The member is anti-aquaporin-4 (AQPR) antibody positive.
B. The member exhibits one of the following core clinical characteristics of NMOSD:
    1. Optic neuritis
    2. Acute myelitis
    3. Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
    4. Acute brainstem syndrome
    5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic magnetic resonance imaging (MRI) lesions
    6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Uplizna.
B. Uplizna is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., reduction in number of relapses).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Uplizna.

2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Uplinza are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the list of core clinical characteristics of NMOSD can be found in the International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (Wingerchuk et al). There are six clinical characteristics cited in the diagnostic criteria:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical
- diencephalic MRI lesions (figure 3)
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

VII. REFERENCES

1. Uplizna [package insert]. Baithersburg, MD: Viela Bio, Inc.; July 2021.
2. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85:177-189.

VABYSMO (faricimab-svoa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Vabysmo is indicated for the treatment of patients with:
A. Diabetic macular edema
B. Neovascular (wet) age-related macular degeneration
C. Macular edema following retinal vein occlusion

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Diabetic Macular Edema[1,2]
Authorization of 6 months may be granted for treatment of diabetic macular edema.

B. Neovascular (Wet) Age-Related Macular Degeneration
Authorization of 6 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

C. Macular Edema Following Retinal Vein Occlusion
Authorization of 6 months may be granted for treatment of macular edema following retinal vein occlusion.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Vabysmo
2. Vabysmo is being used to treat an indication enumerated in Section II
3. The member demonstrated a positive clinical response to therapy (e.g., improvement or maintenance in best corrected visual acuity [BCVA] or vision field, or a reduction in the rate of vision decline or the risk of more severe vision loss).

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Vabysmo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy.
4. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.
5. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusion.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vabysmo are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Vabysmo [package insert]. South San Francisco, CA: Genentech, Inc.; October 2023.
2. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp.
3. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp.
4. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/retinal-vein-occlusions-ppp.

VECTIBIX (panitumumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Vectibix is indicated for the treatment of patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):
1. As first-line therapy in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin).
2. As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

Limitation of Use: Vectibix is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

B. Compendial Use
Colorectal cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Documentation of *RAS* wild-type status or KRAS G12C mutation, where applicable.
B. Documentation of *BRAF* mutation status, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

Colorectal Cancer (CRC)
Authorization of 6 months may be granted for the treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, for unresectable/inoperable, advanced, or metastatic disease and the member has not previously experienced clinical failure on cetuximab when either of the following criteria are met:
1. The member meets all of the following criteria:
   i. The *RAS (KRAS* and *NRAS)* mutation status is negative (wild-type)
   ii. If the tumor is positive for BRAF V600E mutation, the requested medication will be used in combination with encorafenib (Braftovi)
   iii. For first-line treatment of colon cancer, the tumor is left-sided only

OR

2. The member meets all of the following criteria:
   i. The disease is KRAS G12C mutation positive
   ii. The requested medication will be used in combination with sotorasib (Lumakras) or adagrasib (Krazati)
   iii. The member previously received treatment with chemotherapy

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section III when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Vectibix.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Anal Carcinoma
4. NCCN Guideline: Colon Cancer
5. NCCN Guideline: Rectal Cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vectibix are covered in addition to colorectal cancer, including anal adenocarcinoma and appendiceal adenocarcinoma.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Vectibix to treat colorectal cancer, including anal adenocarcinoma and appendiceal adenocarcinoma.can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Vectibix [package insert]. Thousand Oaks, CA: Amgen Inc.; August 2021.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 1.2024. https://www.nccn.org/index.asp. Accessed November 2023.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 4.2023. https://www.nccn.org/index.asp. Accessed November 2023.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 6.2023. https://www.nccn.org/index.asp. Accessed November 2023.

VEOPOZ (pozelimab-bbfg)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Veopoz is indicated for the treatment of adult and pediatric patients 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests: chart notes, medical records and genetic test results documenting:
   1. Confirmed biallelic CD55 loss-of-function mutation
   2. Hypoalbuminemia (serum albumin concentration of ≤3.2 g/dL)
   3. Signs and symptoms of CD-55 PLE (e.g., abdominal pain, diarrhea, peripheral edema, or facial edema)
B. For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

III. CRITERIA FOR INITIAL APPROVAL

CD55-deficient protein-losing enteropathy (PLE)
Authorization of 6 months may be granted for treatment of CD55-deficient protein-losing enteropathy (PLE) when all of the following criteria are met:
A. The member has a confirmed biallelic CD55 loss-of-function mutation detected by genotype analysis
B. The member has hypoalbuminemia (serum albumin concentration of ≤3.2 g/dL)
C. The member has one or more of the following signs and symptoms of CD-55 PLE within the past 6 months:
   1. Abdominal pain
   2. Diarrhea
   3. Peripheral edema
   4. Facial edema

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with Veopoz
   2. Veopoz is being used to treat an indication enumerated in Section III
   3. The member is receiving benefit from therapy (e.g., normalization of serum albumin, improvement in signs and symptoms of disease, and/or decrease in number of hospitalizations and infections)

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Veopoz.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Veopoz are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Veopoz [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; August 2023.

VIDAZA (azacitidine)
azacitidine

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Myelodysplastic syndromes (MDS): azacitidine/Vidaza is indicated for treatment of adult patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).
2. Juvenile myelomonocytic leukemia (JMML): Vidaza is indicated for treatment of pediatric patients aged 1 month and older with newly diagnosed juvenile myelomonocytic leukemia (JMML).

B. Compendial Uses
1. Acute myeloid leukemia (AML)
2. Accelerated phase or blast phase myeloproliferative neoplasm
3. Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
4. Myelodysplastic syndrome (MDS)/Myeloproliferative Neoplasms (MPN) Overlap Neoplasms
5. Peripheral T-cell lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Myelodysplastic syndromes (MDS)
Authorization of 12 months may be granted for the treatment of MDS.

B. Acute myeloid leukemia (AML)
Authorization of 12 months may be granted for the treatment of AML.

C. Accelerated phase or blast phase myeloproliferative neoplasm
Authorization of 12 months may be granted for the treatment of accelerated phase or blast phase myeloproliferative neoplasm.

D. Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Authorization of 12 months may be granted for the treatment of BPDCN when used in combination with venetoclax in either of the following settings:
1. For the treatment of relapsed or refractory disease.
2. For the treatment of systemic disease with palliative intent.

E. Myelodysplastic syndrome (MDS)/Myeloproliferative Neoplasms (MPN) Overlap Neoplasms
Authorization of 12 months may be granted for the treatment of MDS/MPN overlap neoplasms (i.e., chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), BCR-ABL negative atypical chronic myeloid leukemia (aCML), MDS/MPN with neutrophilia, unclassifiable MDS/MPN, MDS/MPN not otherwise specified (NOS), or MDS/MPN with ring sideroblasts and thrombocytosis).

F. Peripheral T-Cell Lymphoma (PTCL)

Authorization of 12 months may be granted for the treatment of peripheral T-cell lymphoma (PTCL) [including the following subtypes: angioimmunoblastic T-cell lymphoma (AITL), nodal peripheral T-cell lymphoma with TFH phenotype (PTCL, TFH), follicular T-cell lymphoma (FTCL)] when all of the following criteria are met:

1. The requested medication will be used as subsequent therapy for relapsed or refractory disease
2. The requested medication will be used as a single agent

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Vidaza
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Acute Myeloid Leukemia
4. NCCN Guideline: Myelodysplastic Syndromes
5. NCCN Guideline: T-Cell Lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vidaza are covered in addition to acute myeloid leukemia (AML), accelerated phase or blast phase myeloproliferative neoplasm, blastic plasmacytoid dendritic cell neoplasm (BPDCN), myelodysplastic syndrome (MDS)/myeloproliferative neoplasms (MPN) overlap neoplasms, and peripheral T-cell lymphoma.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Vidaza to treat acute myeloid leukemia (AML), accelerated phase or blast phase myeloproliferative neoplasm, blastic plasmacytoid dendritic cell neoplasm (BPDCN), myelodysplastic syndrome (MDS)/myeloproliferative neoplasms (MPN) overlap neoplasms, and peripheral T-cell lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Vidaza [package insert]. Summit, NJ: Celgene Corporation; September 2022.
2. Azacitidine injection [package insert]. Princeton, NJ: Sandoz Inc.; September 2022.
3. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc.. Available at http://www.nccn.org. Accessed January 2024.
4. Zoi K, Cross NC. Molecular pathogenesis of atypical CML, CMML and MDS/MPN unclassifiable. Int J Hematol 2015;101:229-242.

VILTEPSO (viltolarsen)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Viltepso is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Viltepso. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 53 skipping (refer to examples in Appendix).
B. Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD).

IV. CRITERIA FOR INITIAL APPROVAL

Duchenne Muscular Dystrophy
Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:
A. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
B. The DMD gene mutation is amenable to exon 53 skipping (refer to examples in Appendix).
C. Treatment with Viltepso is initiated before the age of 10.
D. Member is able to walk independently without assistive devices.
E. Member will not exceed a dose of 80 mg/kg once weekly.
F. The requested medication will not be used concomitantly with golodirsen.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Viltepso.

B. Viltepso is being used to treat an indication enumerated in Section IV.
C. The member is receiving benefit from therapy as evidenced by remaining ambulatory (e.g., not wheelchair dependent).
D. The member will not exceed a dose of 80 mg/kg once weekly.
E. The requested medication will not be used concomitantly with golodirsen.

VI. APPENDIX

Examples of DMD gene mutations (exon deletions) amenable to exon 53 skipping (not an all-inclusive list):

1. Deletion of exon 52
2. Deletion of exon 45-52
3. Deletion of exon 47-52
4. Deletion of exon 48-52
5. Deletion of exon 49-52
6. Deletion of exon 50-52

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Viltepso.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Viltepso are covered.

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

IX. REFERENCES

1. Viltepso [package insert]. Paramus, NJ: NS Pharma, Inc.; March 2021.
2. Watanabe N, Nagata T, Satou Y, et al. NS-065/NCNP-01: An Antisense Oligonucleotide for Potential Treatment of Exon 53 Skipping in Duchenne Muscular Dystrophy. *Mol Ther Nucleic Acids*. 2018;13:442–449. doi:10.1016/j.omtn.2018.09.017.

VIMIZIM (elosulfase alfa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Vimizim is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA, Morquio A syndrome).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: N-acetylgalactosamine-6-sulfatase enzyme assay or genetic testing results supporting diagnosis.
B. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

III. CRITERIA FOR INITIAL APPROVAL

Mucopolysaccharidosis IVA (MPS IVA, Morquio A syndrome)
Authorization of 12 months may be granted for treatment of MPS IVA (Morquio A syndrome) when the diagnosis of MPS IVA was confirmed by enzyme assay demonstrating a deficiency of N-acetylgalactosamine-6-sulfatase enzyme activity or by genetic testing.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Vimizim.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. International guidelines for the management and treatment of Morquio A syndrome.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vimizim are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for confirming the diagnosis with enzyme assays or genetic testing prior to using Vimizim to treat MPS IVA can be found in the guidelines published by Hendriksz et al. A definite diagnosis entails demonstration of reduced N-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts. Molecular analysis can be performed as a further confirmation of the diagnosis.

VII. REFERENCES

1. Vimizim [package insert]. Novato, CA: BioMarin Pharmaceutical Inc.; December 2019.
2. Hendriksz CJ, Berger KI, Giugliani R, et al. International guidelines for the management and treatment of Morquio A syndrome. *Am J Med Genet A*. 2015;167A(1):11-25.

VISUDYNE (verteporfin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis.

B. Compendial Uses
Non-melanoma skin cancer

C. Nationally Covered Indication
CMS covers Visudyne for age-related macular degeneration in specific circumstances. See Section III for more information.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

A. The following exclusion applies to all requests for Visudyne
Use of Visudyne is excluded when it is not used in conjunction with ocular photodynamic therapy or not administered intravenously

B. The following exclusions apply to requests for Visudyne for age-related macular degeneration (AMD)
1. Treatment of juxtafoveal or extrafoveal CNV lesions (lesions outside the fovea)
2. Inability to obtain a fluorescein angiogram
3. Atrophic or “dry” AMD

III. CRITERIA FOR INITIAL APPROVAL

A. Neovascular (wet) age-related macular degeneration
Authorization of 12 months may be granted for treatment of neovascular age-related macular degeneration when any of the following criteria are/is met:
1. The member has predominately classic subfoveal choroidal neovascularization (CNV) lesions, where the area of classic CNV occupies at least 50% of the area of the entire lesion, at the initial visit as determined by a fluorescein angiogram.
2. The member has subfoveal occult with no classic CNV associated with AMD and meets both criteria below:
    i. The lesions are small (4 disk areas or less in size) at the time of initial treatment or within the 3 months prior to initial treatment.
    ii. The lesions have shown evidence of progression within the 3 months prior to initial treatment. Evidence of progression must be documented by deterioration of visual acuity (at least 5 letters on a standard eye examination chart), lesion growth (an increase in at least 1 disk area), or the appearance of blood associated with the lesion.
3. The member has subfoveal minimally classic CNV, where the area occupies less than 50% of the area of the entire lesion, associated with AMD and meets both criteria below:
    i. The lesions are small (4 disk areas or less in size) at the time of initial treatment or within the 3 months prior to initial treatment.

ii. The lesions have shown evidence of progression within the 3 months prior to initial treatment. Evidence of progression must be documented by deterioration of visual acuity (at least 5 letters on a standard eye examination chart), lesion growth (an increase in at least 1 disk area), or the appearance of blood associated with the lesion.

B. Pathologic myopia associated with classic subfoveal choroidal neovascularization
Authorization of 12 months may be granted for treatment of pathologic myopia associated with classic subfoveal choroidal neovascularization.

C. Presumed ocular histoplasmosis associated with classic subfoveal choroidal neovascularization
Authorization of 12 months may be granted for the treatment of presumed ocular histoplasmosis associated with classic subfoveal choroidal neovascularization.

D. Non-melanoma skin cancer
Authorization of 12 months may be granted for the treatment of non-melanoma skin cancer.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with requested medication.
B. None of the exclusions delineated in section II are met.
C. The requested medication is being used to treat an indication enumerated in Section III.
D. The medication has been effective for treating the diagnosis or condition.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Visudyne.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.
4. National Coverage Determination: Verteporfin

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Visudyne are covered in addition to non-melanoma skin cancer.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Visudyne to treat non-melanoma skin cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration is covered according to the conditions outlined in National Coverage Determination Manual section 80.3.1 (Verteporfin).

VII. REFERENCES

1. Visudyne [package insert]. Charleston, SC: Alcami Carolinas Corporation; February 2023.
2. Micromedex Solutions [database online]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/. Accessed February 14, 2023.
3. National Coverage Determination (NCD) for Verteporfin (80.3.1). Version 2. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=350&ncdver=2&DocID=80.3.1&SearchType=Advanced&bc=EAAAAAgAAAAA& Accessed December 11, 2023.
4. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp.

VONVENDI (von Willebrand factor [recombinant])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Vonvendi is indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for:
1. On-demand treatment and control of bleeding episodes
2. Perioperative management of bleeding
3. Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD receiving on-demand therapy

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Von Willebrand Disease
Authorization of 12 months may be granted for members with VWD when any of the following criteria is met:
A. Member has type 1, 2A, 2M, or 2N VWD and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix).
B. Member has type 2B or type 3 VWD.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. Vonvendi is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. APPENDIX

Clinical Reasons for Not Utilizing Desmopressin in Patients with Type 1, 2A, 2M and 2N VWD
A. Age < 2 years
B. Pregnancy
C. Fluid/electrolyte imbalance
D. High risk for cardiovascular or cerebrovascular disease (especially the elderly)
E. Predisposition to thrombus formation
F. Trauma requiring surgery
G. Life-threatening bleed
H. Contraindication or intolerance to desmopressin
I. Severe type 1 von Willebrand disease
J. Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Vonvendi.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. The diagnosis, evaluation, and management of von Willebrand disease.
4. MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vonvendi are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Vonvendi to treat von Willebrand disease can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". Type 2B and type 3 VWD do not respond consistently to DDAVP therapy and therefore DDAVP is not considered clinically useful in these patients.

The guideline from the National Bleeding Disorders Foundation (previously the National Hemophilia Foundation) also recommends using Vonvendi in VWD. Vonvendi is used to treat patients with type 2B and type 3 VWD; it can also be used in patients with types 1, 2A, 2M, and 2N VWD who are not responsive to DDAVP and in children under 2 years of age regardless of VWD type. Vonvendi is approved for use as routine prophylaxis only in individuals with severe type 3 VWD who were previously treated with VWF (recombinant or plasma-derived) on-demand.

VI. REFERENCES

1. Vonvendi [package insert]. Lexington, MA: Baxalta US Inc.; March 2023.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-280-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-selected-disorders-of-the-coagulation-system. Accessed October 5, 2023.
3. National Hemophilia Foundation. MASAC recommendations regarding the treatment of von Willebrand disease. Revised February 2021. MASAC Document #266. https://www.hemophilia.org/sites/default/files/document/files/266.pdf. Accessed October 4, 2022.
4. National Institutes of Health. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007. NIH publication No. 08-5832.
5. Stimate [package insert]. King of Prussia, PA: CSL Behring LLC; June 2021.
6. Leissinger C, Carcao M, Gill JC, et al. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. *Haemophilia*. 2014;20:158-167.

VPRIV (velaglucerase alfa)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
VPRIV is indicated for long-term enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease.

B. Compendial Uses
1. Gaucher disease type 2
2. Gaucher disease type 3

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
For initial requests: beta-glucocerebrosidase enzyme assay or genetic testing results supporting diagnosis.

III. CRITERIA FOR INITIAL APPROVAL

A. Gaucher disease type 1
Authorization of 12 months may be granted for treatment of Gaucher disease type 1 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

B. Gaucher disease type 2
Authorization of 12 months may be granted for treatment of Gaucher disease type 2 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

C. Gaucher disease type 3
Authorization of 12 months may be granted for treatment of Gaucher disease type 3 when the diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy. Benefit is defined as not experiencing an inadequate response or any intolerable adverse events from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for VPRIV.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Gaucher disease: GeneReviews.
4. Revised recommendations for the management of Gaucher disease in children.
5. Management of neuronopathic Gaucher disease: revised recommendations. European Working Group on Gaucher Disease.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for VPRIV are covered in addition to the following:

A. Gaucher disease type 2
B. Gaucher disease type 3

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The diagnosis of Gaucher disease relies on demonstration of deficient glucocerebrosidase (glucosylceramidase) enzyme activity in peripheral blood leukocytes or other nucleated cells or by the identification of biallelic pathogenic variants in *GBA1* (formerly *GBA*). (Pastores and Hughes).

Support for using VPRIV to treat Gaucher disease type 2 can be found in the National Organization for Rare Disorders Guide to Rare Disorders. Enzyme replacement therapy (ERT) is effective for type 1 disease. Anemia and thrombocytopenia improve, hepatomegaly and splenomegaly are reduced, and skeletal damage is ameliorated with ERT. These systemic manifestations also improve with ERT in patients with type 2 and 3 disease. However, it should be noted that ERT does not reverse brain damage in patients with type 2 disease.

Support for using VPRIV to treat Gaucher disease type 3 can be found in the Revised Recommendations for the Management of Gaucher Disease by Kaplan et al. The guideline indicates symptomatic children with types 1 or 3 disease should receive enzyme replacement therapy, which will prevent debilitating and often irreversible disease progression and allow those with non-neuropathic disease to lead normal healthy lives.

VII. REFERENCES

1. VPRIV [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; September 2021.
2. Pastores GM, Hughes DA. Gaucher Disease. 2000 July 27 [Updated March 9, 2023]. In: Adam MP, Everman DB, Mirzaa GM, et al, editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2023.
3. Kaplan P, Baris H, De Meirleir L, et al. Revised recommendations for the management of Gaucher disease in children. *Eur J Pediatr.* 2013;172:447-458.
4. Vellodi A, Tylki-Szymanska A, Davies EH, et al. Management of neuronopathic Gaucher disease: revised recommendations. European Working Group on Gaucher Disease. *J Inherit Metab Dis*. 2009;32(5):660.
5. National Organization for Rare Disorders. (2003). NORD guide to rare disorders. Philadelphia: Lippincott Williams & Wilkins.

VYEPTI (eptinezumab-jjmr)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Vyepti is indicated for the preventive treatment of migraine in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Preventive treatment of migraines
Authorization of 6 months may be granted for preventive treatment of migraines for members 18 years of age or older when either of the following criteria are met:
A. Member has chronic migraine headache defined as 15 to 26 headache days per month, of which at least 8 are migraine days
B. Member has episodic migraine headaches defined as 4 to 14 headache days per month, of which at least 4 are migraine days

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Vyepti
B. Vyepti is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as a reduction in migraine days per month from baseline

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Vyepti.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. The American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyepti are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information. The number of headache days and migraine days are supported by the inclusion criteria of the clinical studies listed in the prescribing information.

VI. REFERENCES

1. Vyepti [package insert]. Bothell, WA: Lundbeck Seattle BioPharmaceuticals, Inc.; October 2022.
2. Ailani J., Burch RC, Robbins MS. The American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice. *Headache*. 2021 Jul;61(7):1021-1039.

VYJUVEK (beremagene geperpavec-svdt)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Vyjuvek is indicated for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial Requests:
1. Medical records documenting clinical manifestations of disease.
2. Genetic test results confirming a mutation in the COL7A1 gene.

III. CRITERIA FOR INITIAL APPROVAL

Dystrophic Epidermolysis Bullosa (DEB)
Authorization of 12 months may be granted for treatment of wounds in members with dystrophic epidermolysis bullosa (DEB) when all of the following criteria are met:
A. Member is 6 months of age or older.
B. Member has clinical manifestations of disease (e.g., extensive skin blistering, skin erosions, scarring).
C. Member has genetic test results confirming a mutation in the COL7A1 gene.
D. Member does not have a history of squamous cell carcinoma in the affected wound(s) that will receive treatment.
E. The requested medication will be administered once weekly to the affected wound(s) by a healthcare professional either at a healthcare professional setting (e.g., clinic) or a home setting.
F. The requested medication will not be administered to wound(s) that are currently healed.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Vyjuvek.
B. The member is receiving benefit from therapy.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Vyjuvek.
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)

c. Lexi-Drugs
d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyjuvek are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Vyjuvek [package insert]. Pittsburgh, PA: Krystal Biotech, Inc.; May 2023.
2. Guide SV, Gonzalez ME, Bağcı IS, et al. Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa. N Engl J Med. 2022;387(24):2211-2219.

VYONDYS 53 (golodirsen)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Vyondys 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Vyondys 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 53 skipping (refer to examples in Appendix).
B. Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD).

IV. CRITERIA FOR INITIAL APPROVAL

Duchenne Muscular Dystrophy
Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:
A. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
B. The DMD gene mutation is amenable to exon 53 skipping (refer to examples in Appendix).
C. Treatment with Vyondys 53 is initiated before the age of 16.
D. Member is able to achieve an average distance of at least 250 meters while walking independently over 6 minutes.
E. Member will not exceed a dose of 30 mg/kg once weekly.
F. The requested medication will not be used concomitantly with viltolarsen.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with Vyondys 53.
B. Vyondys 53 is being used to treat an indication enumerated in Section IV.
C. The member is receiving benefit from therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent).
D. The member will not exceed a dose of 30 mg/kg once weekly.
E. Vyondys 53 will not be used concomitantly with viltolarsen.

VI. APPENDIX

Examples of DMD gene mutations (exon deletions) amenable to exon 53 skipping (not an all-inclusive list):

1. Deletion of exon 52
2. Deletion of exon 45-52
3. Deletion of exon 47-52
4. Deletion of exon 48-52
5. Deletion of exon 49-52
6. Deletion of exon 50-52

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Vyondys 53.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyondys 53 are covered.

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

IX. REFERENCES

1. Vyondys 53 [package insert]. Cambridge, MA: Sarepta Therapeutics; February 2021.
2. Watanabe N, Nagata T, Satou Y, et al. NS-065/NCNP-01: An Antisense Oligonucleotide for Potential Treatment of Exon 53 Skipping in Duchenne Muscular Dystrophy. *Mol Ther Nucleic Acids*. 2018;13:442–449. doi:10.1016/j.omtn.2018.09.017
3. Vyondys 53™ (golodirsen) eDossier. AMCP Formulary Decisions. AmerisourceBergen Corporation. Conshohocken, PA. Available at: www.formularydecisions.com. Accessed April 15, 2020.

VYVGART (efgartigimod alfa-fcab)
VYVGART HYTRULO (efgartigiomod alfa and hyaluronidase-qvfc)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Vyvgart and Vyvgart Hytrulo are indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial requests: chart notes, medical records, or claims history documenting:
   1. Positive anti-acetylcholine receptor (AChR) antibody test
   2. Myasthenia Gravis Foundation of America (MGFA) clinical classification score
   3. MG activities of daily living (MG-ADL) score
   4. Use of an acetylcholinesterase (AChE) inhibitor, steroid, or non-steroidal immunosuppressive therapy (NSIST)
B. For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

III. CRITERIA FOR INITIAL APPROVAL

Generalized myasthenia gravis (gMG)
Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:
1. Anti-acetylcholine receptor (AChR) antibody positive
2. Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV
3. MG activities of daily living (MG-ADL) total score of 5 or more with at least 50% of the score due to non-ocular symptoms
4. On a stable dose of at least one of the following:
   a. Acetylcholinesterase inhibitors (e.g., pyridostigmine)
   b. Steroids (at least 3 months of treatment)
   c. Nonsteroidal immunosuppressive therapy (NSIST) (at least 6 months of treatment) (e.g., azathioprine, mycophenolate mofetil)

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Vyvgart or Vyvgart Hytrulo.

2. Vyvgart or Vyvgart Hytrulo is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity or disease progression while on the current regimen, AND
   b. The member demonstrates a positive response to therapy (e.g., improvement in MG-ADL score, changes compared to baseline in Quantitative Myasthenia Gravis (QMG) total score).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Vyvgart and Vyvgart Hytrulo.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. International consensus guidance for management of myasthenia gravis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyvgart and Vyvgart Hytrulo are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Vyvgart [package insert]. Boston, MA: Argenx US, Inc.; April 2022.
2. Vyvgart Hytrulo [package insert]. Boston, MA: Argenx US, Inc.: June 2023.
3. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2021; 96 (3) 114-122.
4. Howard JF, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2021. 20:526-536.

VYXEOS (daunorubicin and cytarabine liposome)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Vyxeos is indicated for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Newly-diagnosed Therapy-related Acute Myeloid Leukemia (t-AML)
Authorization of 6 months may be granted for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) when all the following are met:
1. The member is 1 year of age or older
2. The provider has verified the member's prior cumulative anthracycline exposure and deemed therapy with Vyxeos necessary and appropriate
3. The member has a baseline left ventricular ejection fraction (LVEF) within normal limits and the patient's LVEF will be reassessed as clinically required

B. Acute Myeloid Leukemia (AML) with Myelodysplasia-related changes (AML-MRC)
Authorization of 6 months may be granted for the treatment AML with myelodysplasia-related changes (AML-MRC) when all the following are met:
1. The member is 1 year of age or older
2. The provider has verified the member's prior cumulative anthracycline exposure and deemed therapy with Vyxeos necessary and appropriate
3. The member has a baseline left ventricular ejection fraction (LVEF) within normal limits and the patient's LVEF will be reassessed as clinically required

III. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Vyxeos.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Acute Myeloid Leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyxeos are covered.

IV. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Vyxeos to treat treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adult and pediatric patients age 1 year and older can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

V. REFERENCES

1. Vyxeos [package insert]. Palo Alto, CA; Jazz Pharmaceuticals, Inc., September 2022. Accessed November 2023.
2. The NCCN Drugs & Biologics Compendium® ©2022 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 2023.

WILATE (von Willebrand factor/coagulation factor VIII complex [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
   1. Wilate is indicated in children and adults with von Willebrand Disease (VWD) for:
      i. On-demand treatment and control of bleeding episodes
      ii. Perioperative management of bleeding
   2. Wilate is indicated in adolescents and adults with hemophilia A for:
      i. Routine prophylaxis to reduce the frequency of bleeding episodes
      ii. On-demand treatment and control of bleeding episodes

B. Compendial Use
   Acquired von Willebrand Syndrome

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Von Willebrand Disease
Authorization of 12 months may be granted for members with VWD when either of the following criteria is met:
1. Member has type 1, 2A, 2M, or 2N VWD and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
2. Member has type 2B or type 3 VWD.

B. Acquired von Willebrand Syndrome
Authorization of 12 months may be granted for treatment of acquired von Willebrand syndrome.

C. Hemophilia A
Authorization of 12 months may be granted for hemophilia A when the requested medication will be used for either of the following:
1. Member has mild disease (see Appendix A) and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
2. Member has moderate or severe disease (see Appendix A).

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Wilate.
B. Wilate is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix A: Classification of Hemophilia by Clotting Factor Level (% Activity) and Bleeding Episodes

Severity	Clotting Factor Level % activity*	Bleeding Episodes
Severe	<1%	Spontaneous bleeding episodes, predominantly into joints and muscles Severe bleeding with trauma, injury or surgery
Moderate	1% to 5%	Occasional spontaneous bleeding episodes Severe bleeding with trauma, injury or surgery
Mild	6% to 40%	Severe bleeding with serious injury, trauma or surgery

*Factor assay levels are required to determine the diagnosis and are of value in monitoring treatment response.

Appendix B: Clinical Reasons For Not Utilizing Desmopressin in Patients with Hemophilia A and Type 1, 2A, 2M and 2N VWD

A. Age < 2 years
B. Pregnancy
C. Fluid/electrolyte imbalance
D. High risk for cardiovascular or cerebrovascular disease (especially the elderly)
E. Predisposition to thrombus formation
F. Trauma requiring surgery
G. Life-threatening bleed
H. Contraindication or intolerance to desmopressin
I. Severe type 1 von Willebrand disease
J. Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Wilate.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. The diagnosis, evaluation, and management of von Willebrand disease.
4. World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, 3rd edition.
5. MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Wilate are covered in addition to acquired von Willebrand syndrome.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Wilate to treat von Willebrand disease can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". Type 2B and type 3 VWD do not respond consistently to DDAVP therapy and therefore DDAVP is not considered clinically useful in these patients. The guideline from the National Bleeding Disorders Foundation (previously the National Hemophilia Foundation) also recommends using Wilate in VWD. Persons with type 2B and type 3 VWD, and those with type 1, 2A, 2M, and 2N who have been shown to be nonresponsive to DDAVP, should be treated with a factor VIII/VWF concentrate (such as Wilate) that is known to contain the higher molecular weight multimers of von Willebrand factor and that has been virally attenuated to eliminate transmission of HIV and hepatitis A, B, and C.

Support for using Wilate to treat acquired von Willebrand syndrome can be found in the National Institutes of Health publication called the “Diagnosis, Evaluation, and Management of von Willebrand Disease”. The guideline indicates DDAVP and Wilate (VWF/FVIII) are first line therapy. If a patient had an inadequate response to DDAVP and VWF/FVIII concentrates, intravenous immunoglobulin given alone was effective in controlling bleeding and raising VWF:RCo activity.

Support for using Wilate to treat hemophilia A can be found in the National Bleeding Disorders Foundation (formerly the National Hemophilia Foundation) MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system. Recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. A possible exception to this recommendation is a newly diagnosed individual, who should also consider with their healthcare providers initiating treatment with a plasma-derived FVIII / von Willebrand Factor (VWF) product.

IV. REFERENCES

1. Wilate [package insert]. Hoboken, NJ: Octapharma USA Inc.; March 2020.
2. National Institutes of Health. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007. NIH publication No. 08-5832.
3. Tiede A, Rand J, Budde U, et al. How I treat the acquired von Willebrand syndrome. *Blood*. 2011;117(25):6777-85.
4. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020 Aug;26 Suppl 6:1-158.
5. Federici A, Budde U, Castaman G, Rand J, Tiede A. Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update. *Semin Thromb Hemost*. 2013;39(2):191-201.
6. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised August 2023. MASAC Document #280. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-280-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-selected-disorders-of-the-coagulation-system. Accessed October 6, 2023.
7. National Hemophilia Foundation. MASAC recommendations regarding the treatment of von Willebrand disease. Revised February 2021. MASAC Document #266. https://www.hemophilia.org/sites/default/files/document/files/66.pdf. Accessed October 6, 2023.
8. Stimate [package insert]. King of Prussia, PA: CSL Behring LLC; June 2021.
9. Leissinger C, Carcao M, Gill JC, et al. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. *Haemophilia*. 2014;20:158-167.

WINREVAIR (sotatercept-csrk)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Winrevair is indicated for the treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) to increase exercise capacity, improve WHO functional class (FC), and reduce the risk of clinical worsening events.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions for initial therapy requests: Chart notes, medical record documentation, or claims history supporting current pulmonary arterial hypertension (PAH) therapy.

III. CRITERIA FOR INITIAL APPROVAL

Pulmonary arterial hypertension (PAH)
Authorization of 12 months may be granted for treatment of PAH in members 18 years of age and older when ALL of the following criteria are met:
1. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).
2. PAH was confirmed by right heart catheterization with all of the following results:
   i. Mean pulmonary arterial pressure (mPAP) > 20 mmHg
   ii. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg
   iii. Pulmonary vascular resistance (PVR) ≥ 5 Wood units while member is stable on at least two PAH medications
3. The requested medication will be used as add-on therapy.
4. Member is currently receiving PAH therapy with medications from at least two of the following drug classes:
   i. Endothelin receptor antagonist (e.g., Letairis, Opsumit, Tracleer)
   ii. Phosphodiesterase-5 inhibitor (e.g., Adcirca, Revatio)
   iii. Soluble guanylate cyclase stimulator (e.g., Adempas)
   iv. Prostacyclin analog (e.g., Flolan, Orenitram, Remodulin, Tyvaso, Veletri, Ventavis)
   v. Prostacyclin receptor agonist (e.g., Uptravi)

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit.

Authorization of 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as either:
   i. Disease stability

ii. Disease improvement

V. APPENDIX

WHO Classification of Pulmonary Hypertension (PH)
1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4. PAH associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 Human immunodeficiency virus (HIV) infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease
- 1.4.5 Schistosomiasis

1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (pulmonary veno-occlusive disease [PVOD]/pulmonary capillary hemangiomatosis [PCH]) involvement
1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
2.1 PH due to heart failure with preserved left ventricular ejection fraction (LVEF)
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
- 4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
- 4.2.2 Other malignant tumors
  - Renal carcinoma
  - Uterine carcinoma
  - Germ cell tumors of the testis
  - Other tumors
- 4.2.3 Non-malignant tumors
  - Uterine leiomyoma
- 4.2.4 Arteritis without connective tissue disease
- 4.2.5 Congenital pulmonary artery stenosis
- 4.2.6 Parasites
  - Hydatidosis

5 PH with unclear and/or multifactorial mechanisms
5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders
5.2 Systemic and metabolic disorders: Pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis
5.3 Others: Chronic renal failure with or without hemodialysis, fibrosing mediastinitis
5.4 Complex congenital heart disease

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Winrevair.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension
4. An overview of the 6th World Symposium on Pulmonary Hypertension
5. Haemodynamic definitions and updated clinical classification of pulmonary hypertension

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Winrevair are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information. Additionally, the haemodynamic definitions and updated clinical classification of pulmonary hypertension indicates pulmonary arterial hypertension (PAH) is best defined by the concomitant presence of mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR ≥ 3 Wood units. A right heart catheterization (RHC) is the diagnostic tool for accurate measurement of these criteria.

Support for using Winrevair as add-on therapy to treat PAH can be found in a study of sotatercept for the treatment of PAH (STELLAR). Hoeper and colleagues conducted the multicenter, double-blind, phase 3 STELLAR trial in adults with PAH (World Health Organization [WHO] functional class II or III) who were receiving stable background therapy. Background therapy referred to approved PAH-specific medications and consisted of monotherapy or combination therapy with endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. To be included in the trial, a diagnostic RHC must have confirmed WHO PAH Group 1 prior to screening. During the screening period, patients needed to have a baseline RHC showing PVR $\geq$ 5 Wood units and a PCWP $\leq$ 15 mmHg. The primary endpoint of the trial was the change from baseline at week 24 in the 6-minute walk distance where the median change in baseline was 34.4 m (95% confidence interval [CI], 33.0 to 35.5) in the sotatercept group and 1.0 m (95% CI, −0.3 to 3.5) in the placebo group. Nine secondary end points, tested hierarchically in the following order, were multicomponent improvement, change in pulmonary vascular resistance, change in N-terminal pro–B-type natriuretic peptide level, improvement in WHO functional class, time to death or clinical worsening, French risk score, and changes in the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) Physical Impacts, Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts domain scores. The first eight secondary end points were significantly improved with sotatercept as compared with placebo, whereas the PAH-SYMPACT Cognitive/Emotional Impacts domain score was not.

VIII. REFERENCES

1. Winrevair [package insert]. Rahway, NJ: Merck Sharp & Dohme LLC; March 2024.
2. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. *N Engl J Med*. 2023;388(16):1478-1490. doi: 10.1056/NEJMoa2213558
3. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. Supplementary appendix. *N Engl J Med*. 2023;Suppl Appendix.
4. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J.* 2019;53(1):1802148. doi: 10.1183/13993003.02148-2018
5. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53(1):1801913. doi:10.1183/13993003.01913-2018
6. Acceleron Pharma, Inc. A Study of Sotatercept for the Treatment of Pulmonary Arterial Hypertension (MK-7962-003/A011-11)(STELLAR). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [4/25/2024]. Available from: https://clinicaltrials.gov/study/NCT04576988. NLM Identifier: NCT04576988.

XENPOZYME (olipudase alfa-rpcp)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Xenpozyme is indicated for treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Initial requests: acid sphingomyelinase enzyme assay supporting the diagnosis.
B. Continuation of therapy requests: documentation (e.g., chart notes, lab results) of a response to therapy (e.g., improvement in lung function, reduction in spleen volume, reduction in liver volume, improvement in platelet count, improvement in linear growth progression).

III. CRITERIA FOR INITIAL APPROVAL

Acid Sphingomyelinase Deficiency (ASMD)
Authorization of 12 months may be granted for treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) when the diagnosis is confirmed by a documented deficiency of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy (e.g., improvement in lung function, reduction in spleen volume, reduction in liver volume, improvement in platelet count, improvement in linear growth progression).

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Xenpozyme.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs

e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xenpozyme are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using an enzyme assay to confirm the diagnosis of ASMD prior to initiating treatment with Xenpozyme can be found in the clinical trials cited in the prescribing information. To be included in the trial, the patient must have had a documented deficiency of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes.

VII. REFERENCES

1. Xenpozyme [package insert]. Cambridge, MA: Genzyme Corporation; July 2023.

XGEVA (denosumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
   2. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
   3. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

B. Compendial Uses
   1. Treatment for osteopenia/osteoporosis in patients with systemic mastocytosis
   2. Thyroid cancer as palliative care for bone metastases

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Multiple myeloma
Authorization of 12 months may be granted for prevention of skeletal-related events in members with multiple myeloma.

B. Bone metastases from a solid tumor
Authorization of 12 months may be granted for either of the following:
1. For prevention of skeletal-related events in members with bone metastases from a solid tumor (e.g., breast cancer, non-small cell lung cancer, thyroid carcinoma, kidney cancer, prostate cancer).
2. As palliative care for bone metastases from thyroid carcinoma.

C. Giant cell tumor of bone
Authorization of 12 months may be granted for treatment of giant cell tumor of bone.

D. Hypercalcemia of malignancy
Authorization of 6 months may be granted for treatment of hypercalcemia of malignancy.

E. Systemic mastocytosis
Authorization of 12 months may be granted for treatment of osteopenia or osteoporosis in members with systemic mastocytosis.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Hypercalcemia of malignancy
Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Xgeva
2. Xgeva is being used to treat hypercalcemia of malignancy

3. The member is receiving benefit from therapy. Benefit is defined as:
    i. Disease stability, or
    ii. Disease improvement

B. All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Xgeva
2. Xgeva is being used to treat an indication enumerated in Section II other than hypercalcemia of malignancy
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. Disease stability, or
    ii. Disease improvement

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Xgeva.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
3. NCCN Guideline: Prostate cancer
4. NCCN Guideline: Multiple myeloma
5. NCCN Guideline: Bone cancer
6. NCCN Guideline: Non-small cell lung cancer
7. NCCN Guideline: Breast cancer
8. NCCN Guideline: Thyroid carcinoma
9. NCCN Guideline: Kidney cancer
10. NCCN Guideline: Systemic mastocytosis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xgeva are covered in addition to the following:

A. Treatment of osteopenia/osteoporosis in patients with systemic mastocytosis
B. Palliative care for bone metastases in thyroid cancer

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Xgeva as treatment for osteopenia or osteoporosis in patients with systemic mastocytosis can be found in the National Comprehensive Cancer Network's guideline for systemic mastocytosis. The NCCN Guideline for systemic mastocytosis supports the use of Xgeva as second-line therapy for osteopenia/osteoporosis in patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.

Support for using Xgeva as palliative care for bone metastases in patients with thyroid cancer can be found in the National Comprehensive Cancer Network's guideline for thyroid carcinoma. The NCCN Guideline for thyroid carcinoma supports the use of Xgeva as care for bone metastases for the following cancer types: papillary carcinoma, follicular carcinoma, oncocytic carcinoma, medullary carcinoma, and anaplastic carcinoma.

VI. REFERENCES

1. Xgeva [package insert]. Thousand Oaks, CA: Amgen Inc.; June 2020.
2. The NCCN Drugs & Biologics Compendium™ © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed October 11, 2023.

XIAFLEX
(collagenase clostridium histolyticum)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. Xiaflex is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord.
B. Xiaflex is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Dupuytren's contracture: Chart notes or medical record indicating the affected joint, contracture, and a positive table top test (for new starts and continuation) and the number of injections the member has received (for continuation only).
B. Peyronie's disease: Chart notes or medical record indicating palpable plaque, curvature, intact erectile function (for new starts and continuation) and the number of injections the member has received (for continuation only).

III. PRESCRIBER SPECIALTIES

A. Dupuytren's contracture: The medication must be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.
B. Peyronie's disease: The medication must be administered by a healthcare provider experienced in the treatment of urological disease and who has completed the Xiaflex REMS program requirements.

IV. EXCLUSIONS

Coverage will not be provided for cosmetic use (e.g., cellulite reduction treatment).

V. CRITERIA FOR INITIAL APPROVAL

A. **Dupuytren's contracture**
Authorization of 6 months may be granted for the treatment of Dupuytren's contracture when the following criteria are met:
1. The member has a finger flexion contracture with a palpable cord in a metacarpophalangeal joint or a proximal interphalangeal joint.
2. The contracture is at least 20 degrees.
3. The member had a positive table top test, defined as the inability to simultaneously place the affected finger(s) and palm flat against a table.
4. The member will receive up to 3 injections maximum per cord (4 weeks apart).

B. **Peyronie's disease**

Authorization of 12 months may be granted for the treatment of Peyronie's disease when the following criteria are met:

1. Xiaflex is prescribed for a member 18 years of age or older with stable Peyronie's disease.
2. The member has a palpable plaque and curvature deformity of at least 30 degrees and less than 90 degrees with intact erectile function (with or without medication) at the start of therapy.
3. The member will receive a maximum of one treatment course or a maximum of 8 injections total, including any injections the member has received for any previous treatment.

VI. CONTINUATION OF THERAPY

Authorization for 6 months (Dupuytren's contracture) or 12 months (Peyronie's disease) to complete a treatment course may be granted for all members (including new members) who are continuing with Xiaflex therapy when the following criteria are met:

A. Xiaflex is requested for treating a diagnosis or condition enumerated in Section V.
B. For Dupuytren's contracture, the member is continuing with a treatment course for the same cord and has received less than 3 injections total. Requests for treatment of a new cord or recurrence in a previously treated cord must meet initial criteria for approval.
C. For Peyronie's disease, the member has not yet completed treatment with the maximum of 8 injections, including any injections the member has received for any previous treatment and curvature deformity is 15 degrees or more.

VII. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Xiaflex.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Peyronie's Disease: AUA Guideline
4. Injectable collagenase clostridium histolyticum for Dupuytren's contracture

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xiaflex are covered.

VIII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for Dupuytren's contracture can be found in a study published in 2009 by the CORD I study group (Hurst et al). The study enrolled 308 patients with joint contractures of 20 degrees or more in this prospective, randomized, double-blind, placebo-controlled, multicenter trial. The primary metacarpophalangeal or proximal interphalangeal joints of these patients were randomly assigned to receive up to three injections of collagenase clostridium histolyticum (at a dose of 0.58 mg per injection) or placebo in the contracted collagen cord at 30-day intervals. One day after injection, the joints were manipulated. The primary end point was a reduction in contracture to 0 to 5 degrees of full extension 30 days after the last injection. Twenty-six secondary end points were evaluated, and data on adverse events were collected. Collagenase treatment significantly improved outcomes. More cords that were injected with collagenase than cords injected with placebo met the primary end point (64.0% vs. 6.8%, $P<0.001$), as well as all secondary end points ($P\leq0.002$). Overall, the range of motion in the joints was significantly improved after injection with collagenase as compared with placebo (from 43.9 to 80.7 degrees vs. from 45.3 to 49.5 degrees, $P<0.001$). The most commonly reported adverse events were localized swelling, pain, bruising, pruritus, and transient regional lymph-node enlargement and tenderness. Three treatment-related serious adverse events were reported: two tendon ruptures and one case of complex regional pain syndrome. No significant changes in flexion or grip strength, no systemic allergic reactions, and no nerve injuries were observed.

According to the prescribing information, four weeks after the initial Xiaflex injection and finger extension procedure, if a contracture remains, the cord may be re-injected with a single dose of 0.58 mg of Xiaflex and the finger extension procedure may be repeated. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.

Support for using Xiaflex for Peyronie's disease can be found in a guideline published by the American Urological Association. The AUA states clinicians may administer intralesional collagenase clostridium histolyticum in combination with modeling by the clinician and by the patient for the reduction of penile curvature in patients with stable Peyronie's disease, penile curvature >30° and <90°, and intact erectile function (with or without the use of medications).
According to the prescribing information, a treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of two XIAFLEX injection procedures and one penile modeling procedure [see Dosage and Administration (2.2)]. The second XIAFLEX injection procedure is performed 1 to 3 days after the first. The penile modeling procedure is performed 1 to 3 days after the second injection of the treatment cycle. The interval between treatment cycles is approximately 6 weeks. The treatment course therefore, consists of a maximum of 8 injection procedures and 4 modeling procedures.

IX. REFERENCES

1. Xiaflex [package insert]. Malvern, PA: Endo Pharmaceuticals Inc.; August 2022.
2. Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. N Engl J Med. 2009;361(10):968-979.
3. Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's Disease: AUA Guideline. *J Urol.* 2015;194(3):745-753.

XIPERE (triamcinolone acetonide injectable suspension)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Xipere is indicated for the treatment of macular edema associated with uveitis.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Macular edema associated with uveitis
Authorization of 12 months may be granted for treatment of macular edema associated with uveitis when all the following criteria are met:

A. The member has a diagnosis of macular edema associated with uveitis.
B. The member does not have infectious uveitis.
C. The member will not exceed a dose of 4 mg (0.1 mL) administered as a suprachoroidal injection per eye into the affected eye(s).

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The medication has been effective for treating the diagnosis or condition

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Xipere.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xipere are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Xipere to treat noninfectious uveitis can be found in a study by Yeh et al. The study enrolled 160 patients with ME secondary to noninfectious uveitis. Patients were required to have a best-corrected visual acuity (BCVA) of 5 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent, 20/800) and 70 or fewer ETDRS letters read (Snellen equivalent, 20/40) in the study eye. Patients were randomized 3:2 to suprachoroidally injected CLS-TA or sham treatment, with administrations at day 0 and week 12. The primary end point was improvement from baseline of 15 or more ETDRS letters in BCVA at week 24. The secondary end point was reduction from baseline in central subfield thickness (CST) at week 24. In the CLS-TA arm, 47% of patients gained 15 or more ETDRS letters in BCVA versus 16% in the control arm ($P < 0.001$), meeting the primary end point. Mean reductions in CST from baseline were 153 μm versus 18 μm ($P < 0.001$). No serious adverse events (AEs) related to treatment were reported. Corticosteroid-associated AEs of elevated intraocular pressure occurred in 11.5% and 15.6% of the CLS-TA and control groups, respectively. Cataract AE rates were comparable (7.3% and 6.3%, respectively).

VI. REFERENCES

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XOLAIR (omalizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Allergic Asthma
   Treatment of moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.

2. Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
   Xolair is indicated for add-on maintenance treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

3. IgE-mediate Food Allergy
   Xolair is indicated for the reduction of allergic reactions (Type 1), including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy.

   Xolair is to be used in conjunction with food allergen avoidance.

4. Chronic Spontaneous Urticaria (CSU)
   Treatment of chronic spontaneous urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.

Limitations of use
1. *Not indicated for relief of acute bronchospasm or status asthmaticus*
2. *Not indicated for the emergency treatment of allergic reactions, including anaphylaxis*
3. *Not indicated for other forms of urticaria*

B. Compendial Uses
1. Prophylaxis of seasonal or perennial allergic rhinitis
2. Latex allergy prophylaxis for patients unable to avoid latex
3. Adjunct to immunotherapy for seasonal allergic rhinitis
4. Immune checkpoint inhibitor-related toxicities
5. Systemic mastocytosis

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Asthma:
1. Initial requests:
   i. Chart notes or medical record documentation showing pre-treatment IgE level.
   ii. Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, documentation of clinical reason to avoid therapy.
2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

B. CRSwNP:
   1. Initial requests:
      i. Chart notes or medical record documentation showing nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) details (e.g., polyps location, size), or Meltzer Clinical Score or endoscopic nasal polyp score (NPS) (where applicable).
      ii. Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.
   2. Continuation Requests: Chart notes or medical record documentation supporting benefit from therapy.

C. IgE-mediated food allergy:
   1. Initial requests: Chart notes, medical record documentation, or laboratory tests showing the following (if applicable):
      i. Pre-treatment allergen-specific IgE level
      ii. Skin-prick test wheal diameter
      iii. Pre-treatment serum IgE level
      iv. Positive result of a physician controlled oral food challenge
      v. History of a systemic reaction to a food
   2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

D. CSU:
   1. Initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried showing an inadequate treatment response to a second-generation H1 antihistamine.
   2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

E. Immune checkpoint inhibiter-related toxicity:
   1. Initial requests: Chart notes or medical record documentation showing pre-treatment IgE level.
   2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

F. Systemic mastocytosis:
   1. Initial requests:
      i. Chart notes or medical record documentation supporting diagnosis of systemic mastocytosis.
      ii. Chart notes, medical record documentation, or claims history of prerequisite therapies (if applicable).
   2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

G. Prophylaxis of seasonal or perennial allergic rhinitis:
   1. Initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried, including response to therapy.
   2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

H. Latex allergy prophylaxis:
   1. Initial requests: Chart notes or medical record documentation of allergy.
   2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

I. Adjunct to immunotherapy:
   1. Initial requests: Chart notes or medical record documentation of immunotherapy use.
   2. Continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. Allergic asthma

Authorization of 12 months may be granted for treatment of allergic asthma when all of the following criteria are met:

1. Member is 6 years of age or older.
2. Member has a history of moderate to severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
   i. Inhaled corticosteroid.
   ii. Additional controller (i.e., long-acting beta$_2$-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline).
3. Member has a positive skin test or in vitro reactivity to at least one perennial aeroallergen.
4. Member has a pre-treatment IgE level greater than or equal to 30 IU/mL.

5. Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire).

B. Chronic rhinosinusitis with nasal polyps (CRSwNP)

Authorization of 12 months may be granted for treatment of CRSwNP when all of the following criteria are met:

1. Member is 18 years of age or older.
2. Member has bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal corticosteroid treatment for at least 2 months unless contraindicated or not tolerated.
3. Member has one of the following:
   i. A bilateral nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) showing polyps reaching below the lower border of the middle turbinate or beyond in each nostril.
   ii. Meltzer Clinical Score of 2 or higher in both nostrils.
   iii. A total endoscopic nasal polyp score (NPS) of at least 5 with a minimum score of 2 for each nostril.
4. Member has symptoms of nasal blockage, congestion or obstruction plus one of the following additional symptoms:
   i. Rhinorrhea (anterior/posterior).
   ii. Reduction or loss of smell.
   iii. Facial pain or pressure.
5. Member will continue to use a daily intranasal corticosteroid while being treated with the requested medication, unless contraindicated or not tolerated.
6. Member will not use the requested medication concomitantly with other biologics indicated for nasal polyps (e.g., Dupixent, Nucala).

C. IgE-mediated food allergy

Authorization of 12 months may be granted for the reduction of IgE-mediated food allergy reactions when all of the following criteria are met:

1. Member is 1 year old or older.
2. The diagnosis of IgE-mediated food allergy has been confirmed by either of the following:
   i. Pre-treatment allergen-specific serum IgE level greater than or equal to 6 IU/mL.
   ii. Skin-prick test (SPC) with wheal diameter greater than or equal to 4 mm.
3. Member has one of the following:
   i. A positive physician controlled oral food challenge (e.g., moderate to severe skin, respiratory, or gastrointestinal [GI] symptoms).
   ii. History of a systemic reaction to a food.
4. Member has a pre-treatment serum IgE level greater than or equal to 30 IU/mL.
5. Member will continue to follow a food-allergen avoidance diet.

D. Chronic spontaneous urticaria (CSU)

Authorization of 12 months may be granted for treatment of chronic spontaneous urticaria when all of the following are met:

1. Member is 12 years of age or older.
2. Member has experienced a spontaneous onset of wheals (hives), angioedema, or both, for at least 6 weeks.
3. Member remains symptomatic despite treatment with a second-generation H_1 antihistamine (e.g., cetirizine, fexofenadine, levocetirizine, loratadine) for at least 2 weeks.
4. Member has been evaluated for other causes of urticaria, including bradykinin-related angioedema and interleukin-1-associated urticarial syndromes (auto-inflammatory disorders, urticarial vasculitis).

E. Immune checkpoint inhibitor-related toxicity

Authorization of 1 month may be granted for treatment of immune checkpoint inhibitor-related toxicity when both of the following are met:

1. The member has a refractory case of immune-therapy related severe (G3) pruritus.
2. The member has elevated IgE levels.

F. Systemic mastocytosis

Authorization of 12 months may be granted for the treatment of systemic mastocytosis when both of the following are met:

1. The major and at least one minor diagnostic criterion for systemic mastocytosis are present or three or more minor diagnostic criteria are present (see Appendix).
2. The requested medication will be used in any of the following treatment settings:
    i. Used as stepwise prophylactic treatment for chronic mast cell mediator-related cardiovascular and pulmonary symptoms when the member has tried both of the following:
        a. H1 blockers and H2 blockers.
        b. Corticosteroids.
    ii. Used for prevention of unprovoked anaphylaxis.
    iii. Used for prevention of hymenoptera or food-induced anaphylaxis, with negative specific IgE or negative skin test.
    iv. Used to improve tolerability of venom immunotherapy.

G. Prophylaxis of seasonal or perennial allergic rhinitis
Authorization of 12 months may be granted for prophylaxis of seasonal or perennial allergic rhinitis in patients who previously had inadequate symptom control with a combination of intranasal steroids and an intranasal antihistamine.

H. Latex allergy prophylaxis
Authorization of 12 months may be granted for the prophylaxis of latex allergy symptoms in patients with a proven latex allergy and who are unable to avoid occupational latex (e.g., healthcare workers).

I. Adjunct to immunotherapy
Authorization of 3 months may be granted as an adjunct to immunotherapy for seasonal allergic rhinitis.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section III.
C. The member is receiving benefit from therapy.
D. The member will not use the requested medication concomitantly with other biologics indicated for asthma or CRSwNP (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire).

V. APPENDIX

2017 WHO Diagnostic Criteria for Systemic Mastocytosis
A. Major Criteria: multifocal, dense infiltrates of mast cells (at least 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs
B. Minor Criteria
    1. In biopsy sections of bone marrow or other extracutaneous organs, greater than 25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology, or greater than 25% of all mast cells in bone marrow aspirate smears are immature or atypical
    2. Detection of an activating point mutation at codon 816 of KIT in the bone marrow, blood, or another extracutaneous organ
    3. Mast cells in bone marrow, blood, or other extracutaneous organs express CD25, with or without CD2, in addition to normal mast cell markers
    4. Serum total tryptase persistently greater than 20 ng/mL (unless there is an associated myeloid neoplasm, in which case this parameter is not valid)

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Xolair.
2. The available compendium

A. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
B. Micromedex DrugDex
C. American Hospital Formulary Service- Drug Information (AHFS-DI)
D. Lexi-Drugs
E. Clinical Pharmacology

3. Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention
4. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program
5. Clinical Practice Guideline: Allergic Rhinitis
6. Omalizumab for the Treatment of Multiple Food Allergies

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xolair are covered in addition to the following:

1. Prophylaxis of seasonal or perennial allergic rhinitis
2. Latex allergy prophylaxis for patients unable to avoid latex
3. Adjunct to immunotherapy for seasonal allergic rhinitis
4. Immune checkpoint inhibitor-related toxicities
5. Systemic mastocytosis

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Xolair for allergic asthma can be found in the manufacturer's prescribing information, the Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention guidelines, and the guideline update from the National Asthma Education and Prevention Program. The prescribing information indicates the minimum labeled age for Xolair is six years of age. Xolair should be used in patients whose symptoms are inadequately controlled with inhaled corticosteroids. According to the 2022 update of the GINA Global Strategy for asthma management and prevention, Xolair should be considered as an add-on therapy that is uncontrolled on other medications such as long-acting beta2-agonists, leukotriene receptor antagonists, tiotropium, or inhaled corticosteroids-formoterol maintenance and reliever therapy (MART).

The prescribing information for Xolair as well as the European Forum for Research and Education in Allergy and Airway Diseases (Bachert et al., 2021) support using Xolair to treat nasal polyps. The prescribing information indicates Xolair should be used to treat chronic rhinosinusitis with nasal polyps in patients 18 years of age and older with inadequate response to nasal corticosteroids (e.g., mometasone). In the CRSwNP Trial cited in the package insert, patients used nasal mometasone for a 5 week run in period as well as during the treatment period with Xolair. Prior to randomization, patients were required to have evidence of bilateral polyps as determined by a nasal polyp score (NPS) ≥ 5 with NPS of 2 in each nostril, despite use of nasal mometasone during the run-in period. NPS was measured via endoscopy and scored (range 0-4 per nostril: 0= no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range 0-8). Patients were furthermore required to have a weekly average of nasal congestion score (NCS) > 1 prior to randomization, despite use of nasal mometasone. The co-primary endpoints in Trials 1 and 2 were NPS and average daily NCS at Week 24. In both trials, patients who received Xolair had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS, than patients who received placebo. The greater improvements in NPS and NCS in the Xolair group compared to the placebo group were observed as early as the first assessment at Week 4 in both studies cited in the prescribing information. Xolair had statistically significant improvements on sense of smell score compared to placebo. Sense of smell was measured by a daily assessment on a 0 to 3 point severity scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). The LS mean difference for change from baseline at Week 24 in sense of smell score in Xolair compared to placebo was -0.3 (95% CI: -0.6, -0.1) in Trial 1 and -0.5 (95% CI: -0.7, -0.2) in Trial 2. Xolair had statistically significant improvements on post-nasal drip compared to placebo. The LS mean difference for change from baseline at Week 24 in post-nasal drip score in Xolair compared to placebo was -0.6 (95% CI: -0.8, -0.3) in Trial 1 and -0.5 (95% CI: -0.8, -0.3) in Trial 2. Xolair had statistically significant improvements on runny nose compared to

placebo. The LS mean difference for change from baseline at Week 24 in runny nose score in Xolair compared to placebo was -0.4 (95% CI: -0.7, -0.2) in Trial 1 and -0.6 (95% CI: -0.9, -0.4) in Trial 2.

Support for using Xolair for the reduction of IgE-mediated food allergy reactions can be found in the manufacturer's prescribing information, and in a double-blind, placebo-controlled trial by Wood et al. (Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy [OIT] in Food Allergic Children and Adults [OUtMATCH] trial). In the OUtMATCH trial, patients administered Xolair subcutaneously every 2 to 4 weeks for a total of 16 to 20 weeks, at the doses and frequency based on body weight and total IgE levels. Prior to randomization, patients were required to have history of an allergy to peanut and at least two other foods in the protocol-specified list (cashew, milk, egg, walnut, wheat, and hazelnut). If the results of skin-prick and laboratory testing confirmed the food allergies, double-blind, placebo-controlled oral food challenges followed. A total of 79 of the 118 participants (67%) who received Xolair were able to consume a single dose of at least 600 mg of peanut protein without dose-limiting symptoms during the post-treatment challenge, as compared with 4 of the 59 participants (6.8%) who received placebo. This phase 3 trial involving patients as young as 1 year of age with multiple food allergies showed that 16 weeks of treatment with Xolair substantially increased threshold reactivity to peanut and multiple other foods to levels that could protect against allergic reactions associated with accidental exposure.

Support for the above criteria for using Xolair to treat chronic spontaneous urticaria can be found in the manufacturer's prescribing information, the 2014 guidelines for the diagnosis and management of acute and chronic urticaria (Bernstein et al., 2014), and the EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. The guidelines differentiate between several different causes of urticaria (autoinflammatory disorders, urticarial vasculitis, HAE) and the treatment for these indications differ from the treatment for chronic spontaneous urticaria. Zuberbier et al. (2018) suggest using 2nd generation H1 antihistamines over 1st generation H1 antihistamines for the treatment of chronic urticaria. Bernstein et al. (2014) indicate patients with episodes of urticaria that last greater than six weeks meet the definition of chronic urticaria. The first step for treating chronic urticaria is monotherapy with second generation antihistamines and avoidance of triggers and relevant physical factors if physical urticaria/angioedema syndrome is present. The second step is dose advancement of the second-generation antihistamine, addition of another antihistamine, addition of an H2-antagonist, addition of a leukotriene antagonist or addition of a 1st generation antihistamine at bedtime. The guideline indicates omalizumab should be used in chronic urticaria refractory to these therapies.

Support for using Xolair for prophylaxis of season or perennial allergic rhinitis can be found in a multicenter, open-label study by Nayak et al. (2003), conducted during ragweed season, 287 patients (aged 12 to 75) received subcutaneous omalizumab 300 mg every 3 (IgE greater than 150 international units/mL) or 4 weeks (IgE less than or equal to 150 international units/mL) for 12 weeks beginning 2 weeks prior to ragweed season. Chlorpheniramine 4 mg and fexofenadine 60 mg was permitted as rescue medicine. Overall use of rescue medicine in both groups was very low, 84 of 287 (29.3%). At least one adverse event occurred in 47.4% of patients; headache, upper respiratory tract infection and viral infection were most commonly reported. There were no severe adverse events related to omalizumab therapy.
In a phase 3, randomized, double-blind, parallel-group design by Chervinsky et al. (2003), efficacy and safety of subcutaneous omalizumab (minimum dose 0.016 mg/kg/IgE (international units/mL) per 4 weeks) was investigated in 289 patients with moderate-to-severe PAR. All patients had a positive skin prick test, total serum IgE level of 30 to 700 international units/mL, and were chronically exposed to dust mites, dog or cat allergens. Patients ranged from 12 to 75 years of age and had the following relevant comorbid conditions: 26% with history of asthma; 17% with history of atopic dermatitis; 58% with history of intranasal steroid use; 37% had attempted desensitizing immunotherapy. Using a mean daily nasal severity score (range, 0 to 3; mean of 4-point scores for sneezing, itchy, runny, and stuffy nose) as the primary efficacy variable and compared to placebo, omalizumab was associated with larger improvements in symptoms at each of the 4-week visits and for the overall 16-week treatment period (p less than 0.001 for each). In addition, treated patients were more likely to shift to a less severe symptom category compared to the established baseline severity rating (p=0.001); symptoms were considered controlled in 28% of those on active treatment vs 10% of those on placebo. In post hoc analysis in subgroups of patients who had either previously failed desensitization or intranasal steroids, the favorable effects of omalizumab on nasal symptoms persisted. Furthermore, treated patients required antihistamines on statistically significantly fewer days than those on placebo (p=0.005), although the clinical and economic merits of the small reduction may be questioned (maximum difference between the range of days of rescue medication use was 1.2 days per month, and the proportion of rescue days reached statistically significant difference only during week 8). Other secondary measures that showed

favorable improvements in the omalizumab group were quality of life measures, including larger differences deemed clinically important, and patients' global evaluation of treatment efficacy. About half of treated patients reported complete control or marked improvement in symptoms, in contrast to that degree of control in only 34% of those on placebo. Omalizumab treatment was well tolerated with the following notable occurrences: 1 patient discontinued the study due to urticaria and 1 patient experienced infectious mononucleosis, although the latter was not attributed to drug therapy. No anti-omalizumab antibodies were detected in patients' sera, and no adverse events suggested drug-induced immunologic reactions.

Support for using Xolair as latex allergy prophylaxis in healthcare workers exposed to latex on a daily basis can be found in a randomized study conducted by Leynadier and colleagues (2004). Sixteen healthcare workers with documented allergy (positive skin prick test response; elevated Ig E serum levels [30 to 700 international units/mL]) were randomized to receive either placebo or omalizumab subcutaneously every 2 to 4 weeks for 16 weeks, after which all patients could continue or start omalizumab therapy for another 16 weeks. Omalizumab was dosed according to body weight and serum IgE levels and ranged from 150 to 750 mg monthly. Efficacy was measured by mean conjunctival challenge test total score, which is the sum (rated from 0, absent to 3, severe) of physician-evaluated eye redness, eyelid swelling, chemosis, and tearing and patient-rated itching (1, mild to 4, incapacitating). A score of 7 or less is considered normal. Mean score from baseline to week 16 decreased significantly in patients receiving omalizumab compared with placebo (from 10 to 5 vs from 9.67 to 9). Overall ocular response rate after 32 weeks, was 93.8% (15 of 16 patients). Furthermore, 11 of 15 patients had negative response to a latex glove challenge after 32 weeks of treatment, with the remaining 4 having a mild response.

Support for using Xolair as an adjunct to immunotherapy for seasonal allergic rhinitis can be found in a 4-arm, double-blind, parallel-group, placebo-controlled trial by Casale et al. (2006). The trial found pretreatment with omalizumab significantly decreases the adverse effects associated with rush immunotherapy. Adult patients (n=159; ages 18 to 50 years) with a minimum 2-year history of ragweed allergic rhinitis and no recent immunotherapy were randomized to receive either immunotherapy and omalizumab, placebo immunotherapy and omalizumab, immunotherapy and placebo omalizumab, or placebo immunotherapy and placebo omalizumab. The dose of omalizumab was 0.016 mg/kg/IgE (international units/mL)/month subcutaneously every 2 to 4 weeks, depending on weight and baseline IgE levels. Rush immunotherapy consisted of ragweed extract in increasing doses up to a maximal dose of 1.2 to 4 mcg Amb a 1 within a 3-hour period, one time. Immunotherapy consisted of weekly short ragweed extract injections in increasing doses over 4 weeks, then 8 weeks of a maintenance dose. Patients in each arm underwent 9 weeks of pretreatment with omalizumab or placebo, followed by rush immunotherapy or placebo. Each arm then underwent 12 weeks in 1 of the 4 treatment arms. Patients that received omalizumab in addition to rush immunotherapy had less adverse effects than patients receiving immunotherapy by itself. In post hoc analysis of the groups receiving rush immunotherapy, the addition of omalizumab was associated with an odds ratio of 0.17 (p=0.026) for anaphylaxis compared to groups not receiving omalizumab. Severity scores during the ragweed season were significantly improved in patients that received both omalizumab and immunotherapy compared to those who received immunotherapy by itself (0.69 vs 0.86; p=0.044)

Support for using Xolair for systemic mastocytosis can be found in the National Comprehensive Cancer Network's guideline for systemic mastocytosis. The NCCN Guideline for systemic mastocytosis supports the use of Xolair as a stepwise prophylactic treatment for chronic mast cell mediator-related cardiovascular and pulmonary symptoms. Xolair can also be used for the prevention of the following: unprovoked anaphylaxis, hymenoptera or food-induced anaphylaxis with negative specific IgE or negative skin test, or to improve tolerance while on immunotherapy.

Support for using Xolair for the management of immunotherapy-related toxicities can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline supports the use of Xolair for the management of refractory cases of immunotherapy-related severe (G3) pruritus with increased IgE levels.

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YERVOY (ipilimumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Unresectable or Metastatic Melanoma
   Yervoy is indicated as a single agent or in combination with nivolumab for the treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older.

2. Adjuvant Treatment of Melanoma
   Yervoy is indicated for the adjuvant treatment of adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

3. Advanced Renal Cell Carcinoma
   Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

4. Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer
   Yervoy, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

5. Hepatocellular Carcinoma
   Yervoy, in combination with nivolumab, is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

6. Metastatic Non-Small Cell Lung Cancer
   a. Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
   b. Yervoy, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.

7. Malignant Pleural Mesothelioma
   Yervoy, in combination with nivolumab, is indicated for first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

8. Esophageal Cancer
   Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

B. Compendial Uses

1. Cutaneous melanoma
2. Uveal melanoma
3. Central nervous system (CNS) brain metastases
4. Colorectal cancer, including appendiceal carcinoma
5. Hepatocellular carcinoma
6. Renal cell carcinoma
7. Non-small cell lung cancer

8. Pleural mesothelioma
9. Peritoneal mesothelioma
10. Small bowel adenocarcinoma
11. Neuroendocrine tumors
    a. Poorly differentiated neuroendocrine carcinoma/large or small cell
    b. Well-differentiated grade 3 neuroendocrine tumors
12. Ampullary adenocarcinoma
13. Esophageal/Esophagogastric Junction Cancers
14. Gastric Cancer
15. Kaposi Sarcoma
16. Bone Cancer
17. Biliary Tract Cancers
    a. Cholangiocarcinoma
    b. Gallbladder Cancer
18. Soft Tissue Sarcoma
    a. Extremity/body wall sarcoma
    b. Head/neck sarcoma
    c. Retroperitoneal/intra-abdominal sarcoma
    d. Rhabdomyosarcoma
    e. Angiosarcoma
19. Merkel Cell Carcinoma
20. Head and Neck Cancer
21. Pancreatic Adenocarcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:

A. Documentation of laboratory report confirming MSI-H or mismatch repair deficient (dMMR) tumor status, where applicable
B. Documentation of molecular testing for EGFR exon 19 deletions or exon 21 L858R mutations and ALK rearrangements, where applicable

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous melanoma

1. Authorization of 12 months may be granted for treatment of unresectable or metastatic disease.
2. Authorization of 12 months may be granted for adjuvant treatment following complete resection or no evidence of disease.
3. Authorization of 12 months may be granted as a single agent for limited resectable local recurrence after prior anti-PD-1 therapy.

B. Central nervous system brain metastases

Authorization of 12 months may be granted for treatment of brain metastases with a diagnosis of melanoma.

C. Pleural or peritoneal mesothelioma

Authorization of 12 months may be granted for treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma, in combination with nivolumab.

D. Renal cell carcinoma

Authorization of 12 months may be granted for treatment of renal cell carcinoma in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

E. Colorectal cancer
Authorization of 12 months may be granted for treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

F. Non-small cell lung cancer
Authorization of 12 months may be granted for treatment of recurrent, advanced, or metastatic non-small cell lung cancer if there are no EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue) and the requested medication will be used in a regimen containing nivolumab.

G. Uveal melanoma
Authorization of 12 months may be granted for treatment of uveal melanoma for unresectable or metastatic disease.

H. Hepatocellular carcinoma
Authorization of 12 months may be granted for treatment of hepatocellular carcinoma in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

I. Small bowel adenocarcinoma
Authorization of 12 months may be granted for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high or mismatch repair deficient tumors, in combination with nivolumab.

J. Ampullary adenocarcinoma
Authorization of 12 months may be granted for treatment of progressive, unresectable, or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma, in combination with nivolumab.

K. Neuroendocrine tumors
Authorization of 12 months may be granted for treatment of neuroendocrine tumors, including poorly differentiated neuroendocrine carcinoma/large or small cell and well-differentiated grade 3 neuroendocrine tumors, in combination with nivolumab.

L. Esophageal and Esophagogastric Junction Cancers
1. Authorization of 12 months may be granted in combination with nivolumab for the treatment of esophageal or esophagogastric junction cancer in members who are not surgical candidates or have unresectable locally advanced, recurrent or metastatic disease.
2. Authorization of 12 months may be granted in combination with nivolumab for neoadjuvant or perioperative treatment of esophageal or esophagogastric junction adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.

M. Gastric Cancer
1. Authorization of 12 months may be granted in combination with nivolumab for treatment of gastric adenocarcinoma in members with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors who are not surgical candidates or have unresectable locally advanced, recurrent or metastatic disease.
2. Authorization of 12 months may be granted in combination with nivolumab for primary, neoadjuvant or perioperative treatment of gastric adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.

N. Kaposi Sarcoma
Authorization of 12 months may be granted in combination with nivolumab for subsequent treatment of relapsed/refractory classic Kaposi Sarcoma.

O. Bone Cancer

Authorization of 12 months may be granted in combination with nivolumab for unresectable or metastatic disease when all of the following are met:
1. Disease has tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors
2. Disease has progressed following prior treatment and has no satisfactory alternative treatment options

P. Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer)
Authorization of 12 months may be granted as subsequent treatment in combination with nivolumab for unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutation burden-high (TMB-H).

Q. Soft Tissue Sarcoma
Authorization of 12 months may be granted in combination with nivolumab for treatment of extremity/body wall sarcomas, head/neck sarcomas and retroperitoneal/intra-abdominal sarcomas, rhabdomyosarcoma and angiosarcoma.

R. Merkel Cell Carcinoma
Authorization of 12 months may be granted as a single agent or in combination with nivolumab for treatment of unresectable, recurrent, or stage IV Merkel cell carcinoma.

S. Pancreatic Adenocarcinoma
Authorization of 12 months may be granted in combination with nivolumab for treatment of locally advanced, metastatic, or recurrent pancreatic adenocarcinoma with tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors.

T. Head and Neck Cancer
Authorization of 12 months may be granted in combination with nivolumab for unresectable, recurrent, persistent, or metastatic non-nasopharyngeal cancer.

IV. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma
Authorization for 12 months (up to 3 years) may be granted for all members (including new members) who are continuing with the requested medication therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used as adjuvant treatment for a member with melanoma.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen and
   b. No evidence of disease progression while on the current regimen.

B. Cutaneous melanoma, renal cell carcinoma, hepatocellular carcinoma, colorectal cancer
Authorization for 12 months (up to 4 doses maximum, if member has not already received 4 doses) may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat cutaneous melanoma, renal cell carcinoma, hepatocellular carcinoma, or colorectal cancer.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen and
   b. No evidence of disease progression while on the current regimen.

C. Non-small cell lung cancer, Esophageal/Esophagogastric Junction Cancers, or pleural mesothelioma
Authorization of 12 months (up to 24 months total) may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.

2. The requested medication is being used to treat non-small cell lung cancer, esophageal cancer, or pleural mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen and
   b. No evidence of disease progression while on the current regimen.

D. All other indications

Authorization of 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat any other indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen and
   b. No evidence of disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Yervoy.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: Neuroendocrine and adrenal tumors
4. NCCN Guideline: Small bowel adenocarcinoma
5. NCCN Guideline: Peritoneal mesothelioma
6. NCCN Guideline: Pleural mesothelioma
7. NCCN Guideline: Cutaneous melanoma
8. NCCN Guideline: Non-small cell lung cancer
9. NCCN Guideline: Hepatocellular carcinoma
10. NCCN Guideline: Uveal melanoma
11. NCCN Guideline: Central nervous system cancers
12. NCCN Guideline: Ampullary adenocarcinoma
13. NCCN Guideline: Colon cancer
14. NCCN Guideline: Rectal cancer
15. NCCN Guideline: Kidney cancer
16. NCCN Guideline: Kaposi sarcoma
17. NCCN Guideline: Biliary tract cancers
18. NCCN Guideline: Soft tissue sarcoma
19. NCCN Guideline: Merkel cell carcinoma
20. NCCN Guideline: Head and neck cancers
21. NCCN Guideline: Esophageal/esophagogastric junction cancers
22. NCCN Guideline: Gastric cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Yervoy are covered in addition to the following:
1. Cutaneous melanoma
2. Uveal melanoma
3. Central nervous system (CNS) brain metastases
4. Colorectal cancer, including appendiceal carcinoma
5. Hepatocellular carcinoma
6. Renal cell carcinoma
7. Non-small cell lung cancer
8. Pleural mesothelioma
9. Peritoneal mesothelioma

10. Small bowel adenocarcinoma
11. Neuroendocrine tumors
12. Ampullary adenocarcinoma
13. Esophageal/esophagogastric junction cancers
14. Gastric Cancer
15. Kaposi sarcoma
16. Bone cancer
17. Biliary tract cancers
18. Soft tissue sarcoma
19. Merkel cell carcinoma
20. Head and neck cancers

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the following indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

1. Cutaneous melanoma
2. Uveal melanoma
3. Central nervous system (CNS) brain metastases
4. Colorectal cancer, including appendiceal carcinoma
5. Hepatocellular carcinoma
6. Renal cell carcinoma
7. Non-small cell lung cancer
8. Pleural mesothelioma
9. Peritoneal mesothelioma
10. Small bowel adenocarcinoma
11. Neuroendocrine tumors
12. Ampullary adenocarcinoma
13. Esophageal/esophagogastric junction cancers
14. Gastric cancer
15. Kaposi sarcoma
16. Bone cancer
17. Biliary tract cancers
18. Soft tissue sarcoma
19. Merkel cell carcinoma
20. Head and neck cancers

Support for using Yervoy to treat Merkel cell carcinoma can be found in the Lexi-Drugs database. Use of information in the Lexi-Drugs database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; February 2023.
2. The NCCN Drugs & Biologics Compendium 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 11, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed December 11, 2023
4. Lexicomp [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/home [available with subscription]. Accessed December 11, 2023.

YESCARTA (axicabtagene ciloleucel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
   2. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
   3. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

   Limitations of use: Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

B. Compendial Uses
   1. Histologic transformation of indolent lymphoma to DLBCL
   2. Human immunodeficiency virus (HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
   3. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
   4. Marginal zone lymphomas (MZL):
      a. Extranodal MZL of the stomach (gastric mucosa associated lymphoid tissue (MALT) lymphoma)
      b. Extranodal MZL of nongastric sites (nongastric MALT lymphoma)
      c. Nodal MZL
      d. Splenic MZL
   5. Pediatric primary mediastinal large B-cell lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following information must be available, upon request, for all submissions:
Chart notes, medical record documentation or claims history supporting previous lines of therapy.

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Primary central nervous system lymphoma
B. Previous treatment course with the requested medication or another CD19-directed chimeric antigen receptor (CAR) T-cell therapy.
C. ECOG performance status greater than or equal to 3 (member is not ambulatory and not capable of all self-care, confined to bed or chair more than 50% of waking hours)
D. Inadequate and unstable kidney, liver, pulmonary or cardiac function
E. Active hepatitis B, active hepatitis C or a clinically significant active systemic infection

F. Active inflammatory disorder

IV. CRITERIA FOR INITIAL APPROVAL

A. Adult Large B-cell Lymphoma

Authorization of 3 months may be granted as treatment of B-cell lymphomas in members 18 years of age or older when either of the following criteria are met:

1. The member has received prior treatment with two or more lines of systemic therapy and has any of the following B-cell lymphoma subtypes:
   i. Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma
   ii. Histologic transformation of indolent lymphomas to DLBCL
   iii. Diffuse large B-cell lymphoma (DLBCL)
   iv. Primary mediastinal large B-cell lymphoma
   v. High-grade B-cell lymphomas (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
   vi. Human immunodeficiency virus (HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
   vii. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
   viii. Follicular lymphoma
   ix. Extranodal marginal zone lymphoma of the stomach (gastric MALT)
   x. Extranodal marginal zone lymphoma of nongastric sites (nongastric MALT)
   xi. Nodal marginal zone lymphoma
   xii. Splenic marginal zone lymphoma
2. The member has received prior treatment with first-line chemoimmunotherapy and has any of the following B-cell lymphoma subtypes:
   i. Diffuse large B-cell lymphoma (DLBCL)
   ii. Primary mediastinal large B-cell lymphoma
   iii. High-grade B-cell lymphomas (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
   iv. Human immunodeficiency virus (HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
   v. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)

B. Pediatric Primary Mediastinal Large B-cell Lymphoma

Authorization of 3 months may be granted for treatment of primary mediastinal large B-cell lymphoma in members less than 18 years of age when the member has received prior therapy with at least two prior chemoimmunotherapy regimens and achieved partial response.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Yescarta.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas
4. NCCN Guideline: Pediatric aggressive mature B-cell lymphomas
5. National Coverage Determination: Chimeric Antigen Receptor (CAR) T-cell Therapy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Yescarta are covered in addition to the following:

1. Histologic transformation of indolent lymphoma to DLBCL
2. Human immunodeficiency virus (HIV)-related B-cell lymphomas (including HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specific)
3. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)
4. Marginal zone lymphomas (MZL):
    a. Extranodal MZL of the stomach (gastric mucosa associated lymphoid tissue (MALT) lymphoma)
    b. Extranodal MZL of nongastric sites (nongastric MALT lymphoma)
    c. Nodal MZL
    d. Splenic MZL
5. Pediatric primary mediastinal large B-cell lymphoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Yescarta to treat compendial uses in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

All FDA-approved indications are covered according to the conditions outlined in National Coverage Determination Manual section 110.24 (Chimeric Antigen Receptor [CAR] T-cell Therapy).

VII. REFERENCES

1. Yescarta [package insert]. Santa Monica, CA: Kite Pharma; November 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 17, 2023.
3. The NCCN Clinical Practice Guidelines in Oncology® B-Cell Lymphomas (Version 2.2023). © 2023 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed April 17, 2023.
4. National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24-Version 1). https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=374&ncdver=1&DocID=110.24&SearchType=Advanced&bc=EAAAAAIAAAAA&. Accessed April 17, 2023.
5. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-2544.

YONDELIS (trabectedin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

B. Compendial Uses
1. Uterine sarcoma
2. Soft tissue sarcoma
    i. Extremity/body wall, head/neck
    ii. Retroperitoneal/intra-abdominal
    iii. Rhabdomyosarcoma
    iv. Solitary fibrous tumor
3. Ovarian cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Soft Tissue Sarcoma

1. Authorization of 12 months may be granted for treatment of liposarcoma or leiomyosarcoma when all of the following criteria are met:
    i. The disease is unresectable or metastatic
    ii. The member has received a prior anthracycline-containing regimen

2. Authorization of 12 months may be granted when used as a single agent for the treatment of myxoid liposarcoma when any of the following are met:
    i. The requested medication will be used as neoadjuvant or adjuvant therapy for retroperitoneal/intra-abdominal sarcoma
    ii. The requested medication will be used as neoadjuvant, adjuvant, or primary therapy for extremity/body wall, head/neck sarcoma

3. Authorization of 12 months may be granted when used as single-agent palliative therapy for the treatment of one of the following:
    i. Solitary fibrous tumor
    ii. Advanced/metastatic pleomorphic rhabdomyosarcoma
    iii. Extremity/body wall, head/neck sarcoma for advanced/metastatic disease with disseminated metastases
    iv. Retroperitoneal/intra-abdominal sarcoma for recurrent unresectable or stage IV disease

4. Authorization of 12 months may be granted when used in combination with doxorubicin for the treatment of leiomyosarcoma when either of the following are met:
    i. The requested medication will be used as first-line treatment for advanced or metastatic therapy.
    ii. The requested medication will be used as alternative systemic therapy for unresectable or progressive disease.

B. Uterine Sarcoma

Authorization of 12 months may be granted as a single-agent for treatment of uterine leiomyosarcoma when all of the following criteria are met:

1. The member has been treated with a prior anthracycline-containing regimen
2. One of the following is met:
    i. The member has known or suspected extrauterine disease
    ii. The disease is not suitable for primary surgery
    iii. The requested medication will be used as additional therapy following total hysterectomy with or without bilateral salpingo-oophorectomy
    iv. The member has resectable isolated metastases and the requested medication will be used postoperatively
    v. The member has unresectable isolated metastases or disseminated disease
    vi. The member has radiologically isolated vaginal/pelvic recurrence

Authorization of 12 months may be granted in combination with doxorubicin for treatment of uterine leiomyosarcoma when all of the following criteria are met:

1. The member has advanced, recurrent, metastatic or inoperable disease.
2. One of the following is met:
    i. The member has known or suspected extrauterine disease
    ii. The disease is not suitable for primary surgery
    iii. The requested medication will be used as additional therapy following total hysterectomy with or without bilateral salpingo-oophorectomy
    iv. The member has resectable isolated metastases and the requested medication will be used postoperatively
    v. The member has unresectable isolated metastases or disseminated disease
    vi. The member has radiologically isolated vaginal/pelvic recurrence

C. Ovarian Cancer

Authorization of 12 months may be granted for treatment of recurrent, platinum-sensitive ovarian cancer when used in combination with pegylated liposomal doxorubicin.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen and
    ii. No evidence of disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Yondelis.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Uterine neoplasms
4. NCCN Guideline: Soft tissue sarcoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Yondelis are covered in addition to the following:

1. Uterine sarcoma
2. Soft tissue sarcoma
3. Ovarian cancer

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Yondelis to treat soft tissue sarcoma and uterine sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Yondelis to treat ovarian cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Yondelis [package insert]. Horsham, PA: Janssen Products, LP; June 2020.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 7, 2023.
3. IBM Micromedex® DRUGDEX ® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com. Accessed: August 7, 2023.

YUTIQ (fluocinolone acetonide intravitreal implant)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Yutiq is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Non-infectious Uveitis (NIU)
Authorization of 12 months may be granted for treatment of chronic non-infectious uveitis when all of the following criteria are met:
1. The member has a diagnosis of chronic non-infectious uveitis affecting the posterior segment of the eye
2. The member does not have an active ocular or periocular infection

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Yutiq.
B. The member is receiving benefit from therapy (e.g. stabilization of visual acuity or improvement in BCVA score when compared to baseline, improvement in vitreous haze score)
C. The member has no evidence of unacceptable toxicity while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Yutiq
2. The available compendium
    a. Micromedex DrugDex
    b. American Hospital Formulary Service- Drug Information (AHFS-DI)
    c. Lexi-Drugs
    d. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Yutiq are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Yutiq [package insert]. Watertown, MA; EyePoint Pharmaceuticals, Inc.; October 2023. Accessed November 2023.

ZALTRAP (ziv-aflibercept)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Zaltrap is indicated for use in combination with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) in patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

B. Compendial Uses
1. Colorectal cancer with unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months, as primary treatment in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan)
2. Colorectal cancer (including anal adenocarcinoma and appendiceal adenocarcinoma), advanced or metastatic disease in combination with irinotecan or with FOLFIRI regimen not previously treated with irinotecan-based therapy, as subsequent therapy for disease progression

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Colorectal cancer (CRC)
Authorization of 12 months may be granted for treatment of advanced or metastatic CRC, including anal adenocarcinoma and appendiceal adenocarcinoma, in combination with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) or in combination with irinotecan.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication in Section II when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Zaltrap.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

3. NCCN Guideline: Anal Carcinoma
4. NCCN Guideline: Colon Cancer
5. NCCN Guideline: Rectal Cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zaltrap are covered in addition to colorectal cancer, including anal adenocarcinoma and appendiceal adenocarcinoma.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Zaltrap to treat colorectal cancer, including anal adenocarcinoma and appendiceal adenocarcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VI. REFERENCES

1. Zaltrap [package insert]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; December 2020.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 3.2023. https://www.nccn.org/index.asp. Accessed November 2023.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 4.2023. https://www.nccn.org/index.asp. Accessed November 2023.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 6.2023. https://www.nccn.org/index.asp. Accessed November 2023.

Zepzelca (lurbinectedin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Zepzelca is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

B. Compendial Uses
1. Relapsed small cell lung cancer
2. Primary progressive small cell lung cancer
3. Ewing sarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Small Cell Lung Cancer
Authorization of 12 months may be granted for subsequent treatment of small cell lung cancer as a single agent in any of the following settings:
1. Relapse following complete or partial response or stable disease with initial treatment
2. Primary progressive disease
3. Metastatic disease following disease progression on or after platinum-based chemotherapy

B. Ewing Sarcoma
Authorization of 12 months may be granted for subsequent treatment of Ewing sarcoma as a single agent for relapsed, progressive, or metastatic disease.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy. Benefit is defined as:
1. No evidence of unacceptable toxicity while on current regimen AND
2. No evidence of disease progression while on current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Zepzelca.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

b. Micromedex DrugDex
c. American Hospital Formulary Service- Drug Information (AHFS-DI)
d. Lexi-Drugs
e. Clinical Pharmacology

3. NCCN Guideline: Small cell lung cancer
4. NCCN Guideline: Bone cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zepzelca are covered in addition to the following:

1. Relapsed small cell lung cancer
2. Primary progressive small cell lung cancer
3. Ewing sarcoma

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Zepzelca to treat small cell lung cancer and Ewing sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Zepzelca is recommended as Subsequent systemic therapy for patients with performance status 0-2 as a single agent for relapse following complete or partial response or stable disease with primary treatment or primary progressive disease.

VI. REFERENCES

1. Zepzelca [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; April 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed July 12, 2023.

ZOLADEX (goserelin acetate)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Prostate cancer
   a. For use in combination with flutamide for the management of locally confined stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with Zoladex and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.
   b. In the palliative treatment of advanced carcinoma of the prostate.
2. Endometriosis
   For the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with Zoladex for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months. (Zoladex 3.6 mg strength only)
3. Endometrial thinning
   For use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding. (Zoladex 3.6 mg strength only)
4. Advanced breast cancer
   For use in the palliative treatment of advanced breast cancer in pre-and perimenopausal women (Zoladex 3.6 mg strength only)

B. Compendial Uses
1. Breast cancer
2. Prostate cancer
3. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
4. Preservation of ovarian function
5. Prevention of recurrent menstrual related attacks in acute porphyria
6. Uterine leiomyomata (fibroids)
7. Treatment of chronic anovulatory uterine bleeding with severe anemia
8. Precocious puberty
9. Salivary gland tumor
10. Uterine sarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Hormone receptor status testing results (where applicable).

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions: Use of the 10.8 mg strength for diagnoses other than prostate cancer, breast cancer, and gender dysphoria (if applicable).

IV. CRITERIA FOR INITIAL APPROVAL

A. Breast Cancer
Authorization of 12 months may be granted for the treatment of hormone receptor-positive breast cancer.

B. Prostate Cancer
Authorization of 12 months may be granted for treatment of prostate cancer.

C. Endometriosis
Authorization of a total of 6 months may be granted to members for treatment of endometriosis.

D. Endometrial-thinning agent
1. Authorization of 2 doses may be granted for endometrial thinning prior to endometrial ablation or resection for dysfunctional uterine bleeding.
2. Authorization of a total of 6 months may be granted for treatment of chronic anovulatory uterine bleeding with severe anemia.

E. Gender Dysphoria
1. Authorization of 12 months may be granted for pubertal hormonal suppression in an adolescent member when all of the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member has reached Tanner stage 2 of puberty or greater.
2. Authorization of 12 months may be granted for gender transition when all the following criteria are met:
   a. The member has a diagnosis of gender dysphoria.
   b. The member will receive the requested medication concomitantly with gender-affirming hormones.

F. Preservation of ovarian function
Authorization of 3 months may be granted for preservation of ovarian function when the member is premenopausal and undergoing chemotherapy.

G. Prevention of recurrent menstrual related attacks in acute porphyria
Authorization of 12 months may be granted for prevention of recurrent menstrual related attacks in members with acute porphyria when the requested medication is prescribed by or in consultation with a physician experienced in the management of porphyrias.

H. Uterine leiomyomata (fibroids)
Authorization of a total of 3 months may be granted for treatment of uterine leiomyomata (fibroids) prior to surgery.

I. Precocious puberty
Authorization of 12 months may be granted for precocious puberty when all the following criteria are met:
1. Member had onset of puberty signs before age two.
2. Precocious puberty is due to hypothalamic hamartoma.

J. Salivary gland tumor
Authorization of 12 months may be granted for treatment of recurrent salivary gland tumor as a single agent when the tumor is androgen receptor positive.

K. Uterine sarcoma
Authorization of 12 months may be granted for treatment of low-grade endometrial stromal sarcoma (ESS), adenosarcoma without sarcomatous overgrowth, or estrogen receptor/progesterone receptor positive (ER/PR+) uterine sarcomas as a single agent.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Breast cancer

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity.

B. Prostate cancer
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy (e.g., serum testosterone less than 50 ng/dL) and has not experienced an unacceptable toxicity.

C. Salivary gland tumor and uterine sarcoma
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy and has not experienced an unacceptable toxicity or disease progression while on the current regimen.

D. Gender dysphoria, precocious puberty
Authorization for 12 months may be granted when all the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The member is receiving benefit from therapy.

E. Endometriosis, endometrial-thinning agent, preservation of ovarian function, prevention of recurrent menstrual related attacks in acute porphyria, uterine leiomyomata (fibroids)
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Zoladex.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline
4. Guidance for GPs and other clinicians on the treatment of gender variant people.
5. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, 8th version.
6. British and Irish Porphyria Network. Best practice guidelines on clinical management of acute attacks of porphyria and their complications

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zoladex are covered in addition to the following:
1. Breast cancer
2. Prostate cancer
3. Gender dysphoria (also known as transgender and gender diverse (TGD) persons)
4. Preservation of ovarian function
5. Prevention of recurrent menstrual related attacks in acute porphyria
6. Uterine leiomyomata (fibroids)
7. Treatment of chronic anovulatory uterine bleeding with severe anemia
8. Precocious puberty
9. Salivary gland tumor
10. Uterine sarcoma

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Zoladex to treat breast cancer and prostate cancer in settings not discussed in the prescribing information can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Zoladex to treat salivary gland tumor and uterine sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Zoladex as an endometrial-thinning agent in patients with chronic anovulatory uterine bleeding with severe anemia. In a study by Vercellini et al, subcutaneous goserelin was found to be effective in the treatment of 23 women with chronic anovulatory uterine bleeding and severe anemia. Goserelin was administered as a 3.6-mg depot injection once a month for 6 months; all patients received ferrous sulfate 150 mg twice daily. By two months, all patients were amenorrheic; spotting was reported on 9 subsequent occasions. Hematologic values, including mean hemoglobin, hematocrit, serum iron and serum ferritin, uniformity normalized after six months of combination therapy with goserelin and supplemental iron. Adverse events included hot flashes (91%), headache (30%), insomnia (26%), paresthesia (17%), joint pain (9%), peripheral edema (9%).

Support for using Zoladex to treat gender dysphoria can be found in the Endocrine Society Clinical Practice guideline for endocrine treatment of gender-dysphoric/gender-incongruent persons. The guidelines support GnRH agonist use in both transgender males and transgender females. Specific products are not listed; therefore, coverage is applied to the entire class of GnRH agonists.

Support for using Zoladex for gender dysphoria can also be found in the World Professional Association for Transgender Health (WPATH). According to the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, prescribing GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (defined as past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy. PATH also recommends beginning pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

WPATH recommends health care professionals prescribe progestins or a GnRH agonist for eligible transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.
WPATH also recommends health care professionals prescribe testosterone-lowering medications (including GnRH agonists) for eligible transgender and gender diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.

Support for using Zoladex for preservation of ovarian function can be found in the ASCO Clinical Practice Guidelines for fertility preservation in patients with cancer. The guideline indicates gonadotropin-releasing hormone receptor agonist therapy may be offered to young women, especially those with breast cancer, in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency when proven fertility preservation methods (i.e., oocyte, embryo, or ovarian tissue cryopreservation) are not feasible. Gonadotropin-releasing hormone receptor agonists should not be used in place of proven fertility preservation methods.

Support for using Zoladex for the prevention of recurrent menstrual-related attacks in acute porphyria can be found in the British and Irish Porphyria Network on clinical management of acute attacks of porphyria and their complications (Stein, et al., 2012). In women with recurrent premenstrual attacks of porphyria, GnRH analogues can be administered to prevent ovulation. A number of preparations are available (busrelin, goserelin, histrelin, leuprorelin or triptorelin) and published studies have reported use of differing regimens,

sometimes in extremely low doses.29,30 As an example, Zoladex 3.6 (containing goserelin acetate 3.6 mg) a long acting analogue of GnRH, can be given as an implant by subcutaneous injection into the anterior abdominal wall every 28 days, with the first injection being given during the first few days of the menstrual cycle. Administration of GnRH analogues may induce a hormone surge that can trigger an acute attack. Side-effects include depression, hot flushes, reduced libido, osteoporosis, and other menopausal symptoms. These can be reduced by use of a low dose estrogen patch. Pretreatment assessment of skeletal health (including bone mineral density [BMD] determination) should be arranged with regular gynecology review and annual BMD while treatment continues. Treatment with GnRH analogues should be reviewed after one year.

Support for using Zoladex to treat uterine leiomyoma can be found in a study by Parazzini et al. A 3-year pilot study suggests that depot goserelin may enable peri-menopausal women (with 1 or more uterine fibroids greater than 10 centimeters, symptomatic menorrhagia lasting 3 months or more, and hemoglobin of 9 g/dL) to postpone or avoid hysterectomy. Enrollees were randomized in a 1:4 ratio to immediate surgery/hysterectomy (n=13) or to goserelin treatment (n=59). Goserelin was given as 3.6-mg depot every 28 days for 4 months. If menorrhagia recurred, patients were given another 3.6-mg depot for a 3-month cycle. The same 3-month cycle could be repeated with recurring menorrhagia; however, after that, surgery/hysterectomy was scheduled. During the 3 years of follow-up after initiation of goserelin, 23 of 59 women (39%) had undergone hysterectomy.
Additionally, a study by Rees, Chamberlain and Gillmer found fewer women required hysterectomies when they underwent endometrial resection after fibroid shrinkage with goserelin than when they were treated with goserelin only (33% vs 8.3%). However, among women who completed the 12-month follow-up, there was no statistical difference between treatments in fibroid regrowth. Twenty-nine premenopausal women with fibroids and uterine sizes between 12- and 16-weeks' gestation were given goserelin 3.6 mg subcutaneously every 28 days for 12 to 20 weeks, until randomization suitability (uterine size less than 345 milliliters). Of the 25 who were randomized to receive no further treatment (group 1) or endometrial resection (group 2), 7 women from group 1 and 1 woman from group 2 failed to complete the trial because of heavy menstrual bleeding; 7 of those underwent hysterectomy and 1 (from group 1) underwent resection. In a comparison of the 6 women of group 1 and the 11 from group 2 who completed the study, there was no statistical difference in median fibroid volume.

Support for using Zoladex to treat precocious puberty can be found in a study by de Brito and colleagues. Gonadotropin releasing hormone agonists (GnRH-a) stopped or regressed secondary sexual characteristics, significantly improved mean height standard deviation for bone age, and suppressed luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in 7 of 8 children with gonadotropin-dependent precocious puberty (GDPP) due to hypothalamic hamartoma. All patients had onset of puberty signs before age 2. Magnetic resonance imaging confirmed the presence of hypothalamic hamartoma. Each patient received either goserelin 3.6 mg intramuscularly or leuprolide acetate 3.75 mg subcutaneously every 4 weeks for 2.7 to 8.4 years. One patient had only a partial response and the treatment was changed to every 3 weeks. One patient developed severe local reaction at the injection site and failed the treatment. GnRH-a arrested and regressed sexual characteristics and suppressed basal and peak LH and FSH levels after GnRH administration in 7 of 8 patients. They also significantly increased the mean height standard deviation for bone age from -0.92 to 1.11 during treatment (p less than 0.05). The hamartomas, ranged in diameter from 5 to 18 millimeters, remained the same size and shape during the follow-up period of 4 to 6 years in 6 patients. Long term GnRH-a treatment was safe and effective in controlling precocious pubertal development in this group of patients.

VIII. REFERENCES

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3. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 6, 2023.
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13. Vercellini P, Fedele L, Maggi R, et al: Gonadotropin releasing hormone agonist for chronic anovulatory uterine bleeding and severe anemia. J Reprod Med 1993; 38:127-129.
14. Parazzini F, Bortolotti A, Chiantera V, et al: Goserelin acetate to avoid hysterectomy in pre-menopausal women with fibroids requiring surgery. Eur J Obstet Gynecol Reprod Biol 1999; 87:31-33.
15. Rees M, Chamberlain P, & Gillmer M: Management of uterine fibroids with goserelin acetate alone or goserelin acetate plus endometrial resection. Gynaecol Endoscopy 2001; 10:33-35.
16. de Brito VN, Latronico AC, Arnhold IJP, et al: Treatment of gonadotropin dependent precocious puberty due to hypothalamic hamartoma with gonadotropin releasing hormone agonist depot. Arch Dis Child 1999; 80:231-234.

Reclast (zoledronic acid)
zoledronic acid

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

A. Treatment and prevention of postmenopausal osteoporosis
B. Treatment to increase bone mass in men with osteoporosis
C. Treatment and prevention of glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months
D. Treatment of Paget's disease of bone in men and women

Limitations of Use: Optimal duration of use has not been determined. For patients of low-risk for fracture, consider drug discontinuation after 3 to 5 years of use.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Treatment and prevention of postmenopausal osteoporosis
Authorization of 12 months may be granted for treatment and prevention of postmenopausal osteoporosis.

B. Increasing bone mass in men with osteoporosis
Authorization of 12 months may be granted for treatment to increase bone mass in men with osteoporosis.

C. Increase bone mass in glucocorticoid-induced osteoporosis
Authorization of 12 months may be granted for treatment and prevention to increase bone mass in glucocorticoid-induced osteoporosis.

D. Treatment of Paget's disease of bone
Authorization of 6 months may be granted for treatment of Paget's disease of bone.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy, except for treatment of Paget's disease of bone, must be currently receiving therapy with Reclast or zoledronic acid.

A. Treatment of Paget's disease of bone
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. All other indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Reclast or zoledronic acid
2. The member is receiving Reclast or zoledronic acid for an indication listed in Section II other than treatment of Paget's disease of bone
3. Reclast or zoledronic acid has been effective for treating the diagnosis or condition

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Reclast and zoledronic acid.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Reclast and zoledronic acid are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Reclast [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2020.
2. Zoledronic acid [package insert]. Princeton, NJ: Fosun Pharma USA Inc.; June 2023.

ZOMETA (zoledronic acid)
zoledronic acid

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Zometa/zoledronic acid is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of greater than or equal to 12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL= Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin [g/dL]).
2. Zometa/zoledronic acid is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Limitations of Use: The safety and efficacy of Zometa/zoledronic acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions have not been established.

B. Compendial Uses
1. Breast cancer
2. Monoclonal gammopathy of uncertain significance, with osteopenia or osteoporosis
3. Osteopenia prophylaxis
   i. Secondary to androgen-deprivation therapy in patients with prostate cancer
   ii. Secondary to hormone therapy in patients with breast cancer
   iii. Secondary to ovarian dysfunction induced by adjuvant chemotherapy
4. Treatment of osteopenia or osteoporosis in patients with systemic mastocytosis
5. Langerhans cell histiocytosis with bone disease
6. Treatment or prevention of osteoporosis during androgen-deprivation therapy (ADT) in prostate cancer patients with high fracture risk

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Hypercalcemia of malignancy
Authorization of 6 months may be granted for treatment of hypercalcemia of malignancy.

B. Multiple myeloma
Authorization of 12 months may be granted for treatment or prevention of skeletal-related events in members with multiple myeloma.

C. Bone metastases from a solid tumor
Authorization of 12 months may be granted for treatment or prevention of skeletal-related events in members with bone metastases from a solid tumor (e.g., breast cancer, non-small cell lung cancer, thyroid carcinoma, kidney cancer, prostate cancer).

D. Breast cancer
Authorization of 12 months may be granted for treatment of breast cancer.

E. Monoclonal gammopathy with osteopenia or osteoporosis

Authorization of 12 months may be granted for treatment of osteopenia or osteoporosis associated with monoclonal gammopathy.

F. Osteopenia prophylaxis

1. Authorization of 12 months may be granted for prophylactic treatment of osteopenia secondary to androgen-deprivation therapy in members with prostate cancer.
2. Authorization of 12 months may be granted for prophylactic treatment of osteopenia secondary to endocrine therapy in members with breast cancer.
3. Authorization of 12 months may be granted for prophylactic treatment of osteopenia secondary to ovarian dysfunction induced by adjuvant chemotherapy.

G. Systemic mastocytosis

Authorization of 12 months may be granted for treatment of osteopenia or osteoporosis in members with systemic mastocytosis.

H. Langerhans cell histiocytosis

Authorization of 12 months may be granted for treatment of Langerhans cell histiocytosis with bone disease.

I. Prostate cancer

Authorization of 12 months may be granted members with prostate cancer for treatment or prevention of osteoporosis during androgen-deprivation therapy (ADT).

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with Zometa or zoledronic acid.

A. Hypercalcemia of malignancy

Authorization for 6 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Zometa or zoledronic acid
2. Zometa or zoledronic acid is being used to treat hypercalcemia of malignancy
3. Zometa or zoledronic acid has been effective

B. All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

1. The member is currently receiving therapy with Zometa or zoledronic acid
2. Zometa or zoledronic acid is being used to treat an indication enumerated in Section II other than hypercalcemia of malignancy
3. Zometa or zoledronic acid has been effective for treating the diagnosis or condition

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Zometa and zoledronic acid.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN guideline: Histiocytic neoplasms
4. NCCN guideline: Prostate cancer
5. NCCN guideline: Multiple myeloma
6. NCCN guideline: Non-small cell lung cancer
7. NCCN guideline: Breast cancer
8. NCCN guideline: Thyroid carcinoma

9. NCCN guideline: Systemic mastocytosis
10. NCCN guideline: Kidney cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zometa and zoledronic acid are covered in addition to the following:

A. Breast cancer
B. Monoclonal gammopathy with osteopenia or osteoporosis
C. Prophylaxis against osteopenia
D. Treatment for osteopenia/osteoporosis in patients with systemic mastocytosis
E. Langerhans cell histiocytosis
F. Treatment or prevention of osteoporosis in patients with prostate cancer receiving androgen deprivation therapy

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Zometa and zoledronic acid in patients with breast cancer can be found in two metanalyses. In a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of bisphosphonate use in women with early breast cancer (26 trials; number of participants = 18,766), overall risk of recurrence of any breast cancer was not significantly reduced. However, there were borderline significant reductions in distant recurrence (10-year risk, 20.4% with bisphosphonates vs 21.8% with control), and breast cancer mortality (10-year risk, 16.6% vs 18.4%, respectively). The effect on distant recurrence was primarily related to a significant reduction in bone recurrence of 17%. In subgroup analysis, risk reductions in recurrence (14%), distant recurrence (18%), bone recurrence (28%), and breast cancer mortality (18%) were highly significant in postmenopausal women who received bisphosphonate treatment compared with controls, but the same benefits were not observed in premenopausal women. No treatment benefit was observed for either menopausal subgroup for first distant recurrence at sites other than bone. Benefits for bone recurrence were similar between the non-aminobisphosphonate, clodronate, and the 2 most widely tested aminobisphosphonates, zoledronic acid and ibandronate. The majority (97%) of women were in trials lasting 2 to 5 years and the median follow-up period was 5.6 woman-years.
In a systematic review and meta-analysis, adjuvant zoledronic acid therapy compared with nonuse, placebo, or delayed use, significantly reduced the risk of death by 19% (5 studies, 6414 patients) and the risk of fracture by 21% (7 studies, 7967 patients). However, therapy did not significantly affect disease-free survival, locoregional or distant recurrence, or the incidence of bone metastases. Osteonecrosis of the jaw developed in 0.52% of patients with zoledronic acid and 0% of patients in control groups.

Support for using Zometa and zoledronic acid for treatment of breast cancer can be found in the National Comprehensive Cancer Network's guideline for breast cancer. The NCCN Guideline for breast cancer supports the use of Zometa and zoledronic acid in postmenopausal patients with ductal carcinoma in situ (DCIS) receiving adjuvant aromatase inhibitor therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce the risk of fractures. In patients with invasive breast cancer, Zometa and zoledronic acid can be used in postmenopausal patients receiving adjuvant therapy along with calcium and vitamin D supplementation to either: a) maintain or improve bone mineral density and reduce the risk of fractures or b) for risk reduction of distant metastases for three to five years in high-risk node negative or node positive tumors. In patients with invasive breast cancer or inflammatory breast cancer, Zometa and zoledronic acid can be used with calcium and vitamin D supplementation in addition to systemic therapy or endocrine therapy for bone metastases in patients with an expected survival of at least three months and adequate renal function. In patients with inflammatory breast cancer, Zometa and zoledronic acid can be considered in postmenopausal patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures.

Support for using Zometa and zoledronic acid in monoclonal gammopathy of uncertain significance can be found in a study of 54 patients with monoclonal gammopathy of undetermined significance with osteopenia or osteoporosis by Berenson et al. Treatment with zoledronic acid significantly improved lumbar-spine bone mineral density (BMD) in patients with monoclonal gammopathy of undetermined significance (MGUS) in a open-label, single-arm, phase 2 study (n=54). Patients (median age, 67 years; range, 50 to 91 years)

diagnosed with monoclonal gammopathy of undetermined significance with osteopenia or osteoporosis at the lumbar-spine (LS) or total hip (TH) (defined as a T-score less than -1), a Karnofsky Performance Status score of greater than 60%, no evidence of lytic lesions, anemia, hypercalcemia or renal insufficiency related to the M protein were eligible for the study. Enrolled patients were scheduled to receive zoledronic acid 4 mg IV infusion over 15 minutes on day 0 and repeated at 6 and 12 months. The median baseline LS-BMD T-score was -1.7 (range, -3.97 to +2.1), and the median TH-BMD T-score at baseline was -1.65 (range, -3.5 to +1.4). The primary endpoint was the percent change from baseline (compared with 13 months) in the postero-anterior lumbar-spine (LS) bone mineral density (BMD) T-scores. Although the a priori sample size was planned to be 80 patients, the study was closed early due to difficulty in enrolling patients. Of the 54 patients enrolled, 10 patients (including 6 patients who discontinued) were not evaluable for efficacy due to lack of LS-BMD or TH-BMD assessments at final follow-up. Among the evaluable patients (n=44) after 13 months of treatment, the median percent improvement of the LS-BMD T-score was +21.8% with a median change from baseline of +0.3 (range, -0.38 to +3.91; p less than 0.0001). In the subset group of patients with osteopenia or osteoporosis (n=32), the median percent improvement of the LS-BMD T-score was +16.2% with a median change from baseline of +0.3 (range, -0.38 to +3.91; p less than 0.0021). The TH-BMD T-scores in the group of evaluable patients (n=44) did not show significant change from baseline (median change, +0.19; range, -2.4 to +2.03; p=0.1684). However, in patients with osteopenia or osteoporosis (n=33), the median percent improvement of the TH-BMD T-score (secondary endpoint) was statistically significant at +8.7% with a median change from baseline of +0.2 (range, -0.6 to +2.03; p less than 0.002). The most commonly reported adverse events were fatigue, arthralgia, fever, and generalized hurt. Six patients discontinued the study due to consent withdrawal, 1 death (cause of death unknown), arthralgia, physician's request, progression to chronic lymphocytic leukemia, and development of primary amyloidosis. There were no reports of osteonecrosis of the jaw, new fractures, or progression to multiple myeloma.

Support for the use of Zometa and zoledronic acid to prevent osteopenia in patients receiving androgen deprivation therapy for nonmetastatic prostate cancer can be found in a randomized, double-blind, placebo-controlled, multicenter trial by Smith et al. Zoledronic acid increased bone mineral density (BMD) significantly in the hip and spine in men receiving androgen deprivation therapy (ADT) for prostate cancer. One hundred six men with nonmetastatic prostate cancer (stage M0) were randomized to receive zoledronic acid 4 mg (n=55) IV over 15 minutes every 3 months or placebo (n=51) for 1 year. Analysis of primary efficacy variables were preplanned in 4 subgroups; patients receiving a gonadotropin-releasing hormone (Gn-RH) agonist alone, receiving a Gn-RH agonist and antiandrogen, baseline BMD T-score -1 or greater, and baseline BMD T-score less than -1 to-3. By week 12, mean total testosterone decreased to castrate level (less than 50 nanograms/deciliter). All patients were instructed to take calcium 500 mg and multivitamin containing 400 international units of vitamin D daily. Forty-seven patients in the zoledronic acid group and 43 in the placebo group completed the trial. Lumbar spine BMD in the zoledronic group was increased from baseline at 1 year compared with a decrease of BMD in the placebo group; this change reflected a mean percent change at 1 year between the groups of 7.8% (95% CI, 5.6% to 10%; p less than 0.001). Zoledronic acid was effective regardless of ADT regimen. Intragroup comparisons from baseline were found to be statistically significant: the lumbar spine BMD in the zoledronic group increased 5.6% from baseline (p less than 0.001) and decreased 2.2% from baseline (p=0.0012) in the placebo group. Subgroup analysis of patients with normal baseline lumbar spine BMD and those with low baseline lumbar spine BMD also demonstrated a significant difference in change between the zoledronic acid and placebo groups. Significant hip BMD increases were seen in the zoledronic acid group in the femoral neck, trochanter, and total hip with corresponding decreases seen in the placebo group (femoral neck mean differences, 3.3%, 95% CI, 1.4 to 5.2, p less than 0.001; trochanter mean differences, 4.9%, 95% CI, 2.9 to 6.9, p less than 0.001; and total hip mean differences, 3.9%, 95% CI, 2.5 to 5.3, p less than 0.001, respectively. Differences noted in the nondominant forearm were not statistically significant. Grade 3 or 4 toxicities were reported in both groups; 24% in the zoledronic group and 39% in the placebo group. Five patients withdrew from the study due to adverse effects (3 from the zoledronic group and 2 from the placebo group). The most common toxicities reported in the zoledronic and placebo groups, respectively, were hot flushes (58% vs 51%), fatigue (38% vs 35%), arthralgias (22% vs 14%), constipation (16% in each group), and urinary frequency (15% vs 22%).
Support for using Zometa and zoledronic acid to prevent osteopenia in patients receiving hormone therapy for breast cancer can be found in an open-label, multicenter, randomized, phase 3, (ZO-FAST) trial (n=1065). Improvement in lumbar spine bone mineral density (BMD) was maintained in postmenopausal women with hormone receptor-positive early-stage breast cancer receiving adjuvant letrozole who were treated with immediate compared with delayed zoledronate therapy. This trial enrolled postmenopausal women with hormone-responsive stage I, II, or IIIA breast cancer with Eastern Cooperative Oncology Group (ECOG) scores less than or equal to 2 and baseline lumbar spine and total hip T-scores greater than or equal to -2.

Women with preexisting lumbar spine or hip fractures or with a history of low-intensity fractures were excluded. All patients received letrozole 2.5 mg orally daily for a median of 60 months (range, 0 to 67.8 months) and were randomized to either immediate (initiated within 1 month of randomization) or delayed (only initiated if the patient had a fracture or a decrease in T-score to less than -2) zoledronate 4 mg IV every 6 months. In the immediate group (n=532), a median of 11 infusions of zoledronate were administered to each patient. In the delayed group (n=533), 144 (27%) patients began zoledronate therapy at a median of 12.8 months. At 60 months, mean lumbar spine BMD was increased by 4.3% in the immediate-zoledronate group compared with a 5.4% decrease in the delayed-zoledronate group (p less than 0.0001). In recently postmenopausal women, lumbar spine BMD was preserved, but not improved, in the immediate zoledronate group and was significantly decreased in the delayed zoledronate group (change compared with baseline, -0.3% [p=0.7] and -9.3% [p less than 0.0001], respectively; treatment difference, 9%). However, in established postmenopausal patients, lumbar spine BMD was significantly improved with immediate treatment (change compared with baseline, 5.3%; p less than 0.0001), and was decreased in the delayed-treatment group (change compared with baseline, -4.2%; p less than 0.0001; treatment difference, 9.5%). In analysis of a secondary endpoint, the immediate-zoledronate group had a statistically significant reduction of 34% in risk of disease-free survival events (defined as disease recurrence or death) compared with those in the delayed-zoledronate group (hazard ratio, 0.66; 95% CI, 0.44 to 0.97; p=0.0375).

In an open-label, multicenter, randomized (n=602) study, zoledronic acid given upfront compared with delayed administration prevented cancer treatment-induced bone loss (CTIBL) in postmenopausal women (PMW) with early breast cancer receiving adjuvant letrozole (Let). The Zometa-Femara Adjuvant Synergy Trial (Z-FAST), enrolled PMW with stage I-IIIa estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer and baseline lumbar spine (LS) and total hip (TH) T-scores of -2 or greater. Patients were randomized to receive Let 2.5 mg orally once daily for 5 years with either upfront zoledronic acid 4 mg IV infusion every 6 months (n=301; median age, 60 years; range, 35 to 83 years) or delayed zoledronic acid 4 mg IV infusion every 6 months (n=301; median age, 60 years; range, 41 to 89 years) initiated when either LS and TH T-scores decreased to less than -2 or a nontraumatic fracture occurred. All patients received daily calcium 1000 to 1200 mg and vitamin D 400 to 800 international units. At 12 months, zoledronic acid had been administered to 25 (8.3%) patients (mean time to zoledronic acid initiation, 8.8 months; range, 0.03 to 24.15 months) in the delayed zoledronic acid group. Of 500 evaluable patients, the upfront zoledronic acid group had a positive percent change in bone mineral density (BMD) and the delayed zoledronic acid group had a negative percent change in BMD with an overall BMD mean percent difference between the groups of 4.4% (95% CI, 3.7% to 5%; p less than 0.0001) for LS (primary endpoint) and 3.3% (95% CI, 2.8% to 3.8%; p less than 0.0001) for TH after 12 months of treatment. In a subset of 212 patients, the difference in percent change of serum bone turnover markers between the upfront and delayed zoledronic acid groups was -35% for N-telopeptide (NTx) and -33% for bone-specific alkaline phosphatase (BSAP) at 12 months, with both markers significantly increasing over baseline in the delayed zoledronic acid group (NTx, p less than 0,0001; BSAP, p=0.0006) and significantly decreasing over baseline in the upfront zoledronic acid group (NTx, p=0.013; BSAP, p less than 0.0001). In 300 patients evaluated in the safety analysis, the incidence of adverse events and treatment-related withdrawals were similar between groups; however, bone pain occurred more frequently in the upfront zoledronic acid group compared with the delayed zoledronic acid group (11.3% vs 4%). No patients developed significant renal dysfunction (grade 3 or 4) or jaw osteonecrosis. One patient in the upfront zoledronic acid group developed a grade 1 increase in serum creatinine.

A randomized, phase 3, open-label, prospectively defined bone mineral density (BMD) subprotocol analysis (n=401) in premenopausal women on adjuvant endocrine therapy demonstrated that the addition of zoledronic acid prevented cancer treatment-induced bone loss (CTIBL) compared with patients on adjuvant endocrine therapy alone. Patients with stage I to II, estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer with no prior adjuvant therapy were randomized to subcutaneous (subQ) goserelin 3.6 mg every 28 days and tamoxifen 20 mg orally daily with (n=100; median age, 43.8 years (yr)) or without (n=103; median age, 46.6 yr) IV zoledronic acid 4 mg every 6 months or goserelin 3.6 mg subQ every 28 days and anastrozole 1 mg orally daily with (n=104; median age, 44.7 yr) or without (n=94; median age, 45.7 yr) zoledronic acid 4 mg IV every 6 months. At 36 months, results from 114 patients showed that the treatment groups without zoledronic acid had significant decreases in BMD (lumbar spine observed data, -14.4%, p less than 0.0001; trochanter observed data, -8.2%, p=0.0005) and T-scores (lumbar spine observed mean difference, -1.4, p less than 0.0001; trochanter observed mean difference, -0.6, p=0.0017) compared with baseline. In the treatment groups containing zoledronic acid, BMD remained stable compared with baseline and T-scores significantly improved (p less than 0.0001) compared with adjuvant endocrine therapy alone. Patients receiving the combination of anastrozole and goserelin had significantly greater (p less than 0.0001) overall BMD loss compared with patients receiving tamoxifen and goserelin (lumbar spine observed data, -17.4% vs -11.6%; trochanter observed data, -11.3% vs -5.1%). T-score changes over baseline were greater for the

anastrozole/goserelin group (lumbar spine observed mean difference, -2.6; trochanter observed mean difference, -0.8) compared with the tamoxifen/goserelin group (lumbar spine observed mean difference, -1.1; trochanter observed mean difference, -0.1). Adverse events were mild to moderate in severity and were consistent with known toxicities associated with each drug. Zoledronic acid use was not associated with renal dysfunction and the addition of zoledronic acid did not add significant toxicity to the other treatment groups. No patient experienced bone fractures or jaw osteonecrosis.

Support for using Zometa and zoledronic acid as prophylactic treatment of osteopenia secondary to ovarian dysfunction induced by adjuvant chemotherapy is supported by a prospective study (n=404) of a randomized, open-label, phase 3 study (n=1803) (Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12)). Premenopausal women (19 years or older) who underwent surgery for stage I/II estrogen receptor-positive or progesterone-receptor-positive (or both) breast cancer, had a Karnofsky Index of 70 or greater, had fewer than 10 positive lymph nodes, and were scheduled to receive goserelin for 3 years were stratified by tumor stage and grade, hormone-receptor status, and lymph node involvement, and subsequently randomized to 1 of 4 treatments. The treatment regimens were 3 years of either goserelin 3.6 mg subQ every 28 days plus tamoxifen 20 mg/day orally with or without zoledronic acid 4 mg IV every 6 months or goserelin 3.6 mg subQ every 28 days plus anastrozole 1 mg/day orally with or without zoledronic acid 4 mg IV every 6 months. The median follow-up was 60 months (range, 15.5 to 96.6 months). After 3 years of treatment, endocrine therapy alone caused significant loss of BMD at the lumbar spine (-11.3%, mean difference -0.119 g/cm(2) [95% CI -0.146 to -0.091], p<0.0001) and trochanter (-7.3%, mean difference -0.053 g/cm(2) [-0.076 to -0.030], p<0.0001). In patients who did not receive zoledronic acid, anastrozole caused greater BMD loss than tamoxifen at 36 months at the lumbar spine (-13.6%, mean difference -0.141 g/cm(2) [-0.179 to -0.102] vs -9.0%, mean difference -0.095 g/cm(2) [-0.134 to -0.057], p<0.0001 for both). 2 years after the completion of treatment (median follow-up 60 months [range 15.5-96.6]), patients not receiving zoledronic acid still had decreased BMD at both sites compared with baseline (lumbar spine -6.3%, mean difference -0.067 g/cm(2) [-0.106 to -0.027], p=0.001; trochanter -4.1%, mean difference -0.03 g/cm(2) [-0.062 to 0.001], p=0.058). Patients who received zoledronic acid had stable BMD at 36 months (lumbar spine +0.4%, mean difference 0.004 g/cm(2) [-0.024 to 0.032]; trochanter +0.8%, mean difference 0.006 g/cm(2) [-0.018 to 0.028]) and increased BMD at 60 months at both sites (lumbar spine +4.0%, mean difference 0.039 g/cm(2) [0.005-0.075], p=0.02; trochanter +3.9%, mean difference 0.028 g/cm(2) [0.003-0.058], p=0.07) compared with baseline. Although there was partial recovery 2 years after completing treatment, patients receiving endocrine therapy alone did not recover their baseline BMD levels. Concomitant zoledronic acid prevented bone loss during therapy and improved BMD at 5 years.

Support for using Zometa and zoledronic acid to treat osteoporosis and osteopenia in patients with systemic mastocytosis can be found in the National Comprehensive Cancer Network's guideline for systemic mastocytosis. The NCCN Guideline for systemic mastocytosis supports the use of Zometa when used for the treatment of osteoporosis or osteopenia.

Support for using Zometa and zoledronic acid for Langerhans cell histocytosis can be found in the National Comprehensive Cancer Network's guideline for histiocytic neoplasms. The NCCN Guideline for histiocytic neoplasms supports the use of Zometa and zoledronic acid as preferred first-line or subsequent therapy for unifocal Langerhans cell histiocytosis with isolated bone disease or multifocal bone disease.

Support for using Zometa and zoledronic acid for prevention or treatment of osteoporosis in patients with prostate cancer receiving androgen deprivation therapy can be found in the National Comprehensive Cancer Network's guideline for prostate cancer. The NCCN Guideline for prostate cancer supports the use of Zometa and zoledronic acid to prevent or treat osteoporosis during androgen deprivation therapy in patients with high fracture risk. Zometa and zoledronic acid can also be used to prevent skeletal-related events in patients with castration resistant prostate cancer who have documented bone metastases and a creatinine clearance greater than 30 mL/min.

Support for using Zometa and zoledronic acid for kidney cancer can be found in the National Comprehensive Cancer Network's guideline for kidney cancer. The NCCN Guideline for kidney cancer supports the use of Zometa and zoledronic acid as a component of best supportive care for bony metastases.

Support for using Zometa and zoledronic acid for non-small cell lung cancer can be found in the National Comprehensive Cancer Network's guideline for non-small cell lung cancer. The NCCN Guideline for non-small cell lung cancer supports the use of Zometa and zoledronic acid in those with bony metastases.

Support for using Zometa and zoledronic acid for thyroid carcinoma can be found in the National Comprehensive Cancer Network's guideline for thyroid carcinoma. The NCCN Guideline for thyroid carcinoma supports the use of Zometa and zoledronic acid in papillary carcinoma, follicular carcinoma, oncocytic carcinoma, and medullary carcinoma in patients with bony metastases. In patients with anaplastic carcinoma, Zometa and zoledronic acid can be used as palliative care for bone metastases.

VI. REFERENCES

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10. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol*. 2007;25(7):829-836.
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ZOLGENSMA (onasemnogene abeparvovec-xioi)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Zolgensma is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene.

Limitations of use:
- The safety and effectiveness of repeat administrations of Zolgensma have not been evaluated.
- The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: genetic testing results demonstrating bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy.

IV. CRITERIA FOR INITIAL APPROVAL

Spinal muscular atrophy
Authorization of one dose total may be granted for treatment of spinal muscular atrophy when all of the following criteria are met:
A. Member has a genetically confirmed diagnosis of SMA, with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene (deletions or point mutations).
B. Member is less than 2 years of age.
C. If the member is on nusinersen (Spinraza) or risdiplam (Evrysdi), it will be discontinued prior to administration of the requested drug.
D. The member has not received Zolgensma previously.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Zolgensma.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)

d. Lexi-Drugs
e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zolgensma are covered.

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VII. REFERENCES

1. Zolgensma [package insert]. Bannockburn, IL. Novartis Gene Therapies, Inc; February 2023.

ZYNLONTA (loncastuximab tesirine-lpyl)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Zynlonta is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

B. Compendial Uses
1. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
2. Human immunodeficiency virus (HIV)-related B-cell lymphomas

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions: Chart notes, medical record documentation or claims history supporting previous lines of therapy.

III. CRITERIA FOR INITIAL APPROVAL

A. **Large B-cell lymphoma**
Authorization of 12 months may be granted for treatment of relapsed, progressive or refractory large B-cell lymphoma (e.g., DLBCL NOS, DLBCL arising from low grade lymphoma, high-grade B-cell lymphoma) when all of the following criteria are met:
1. The member has received two or more prior lines of systemic therapy.
2. The requested medication will be used as a single agent.

B. Histologic Transformation of Indolent Lymphomas to Diffuse Large B-cell Lymphoma
Authorization of 12 months may be granted for treatment of histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma when all of the following criteria are met:
1. The requested medication will be used as subsequent therapy.
2. The member is not a candidate for transplant.

C. HIV-Related B-cell lymphomas
Authorization of 12 months may be granted for treatment of relapsed, progressive or refractory HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma when all of the following criteria are met:
1. The member has received two or more lines of systemic therapy.
2. The requested medication will be used as a single agent.

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen, and
    b. No evidence of disease progression while on the current regimen

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Zynlonta.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zynlonta are covered in addition to the following:
1. Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
2. HIV-related B-cell lymphomas

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Zynlonta to treat histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for Zynlonta to treat HIV-related B-cell lymphomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Zynlonta [package insert]. Murray Hill, NJ: ADC Therapeutics America; October 2022.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed April 5, 2023.

ZYNTEGLO (betibeglogene autotemcel)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Zynteglo is indicated for the treatment of adult and pediatric patients with beta-thalassemia who require regular blood cell (RBC) transfusions.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Molecular or genetic testing results documenting transfusion-dependent beta-thalassemia genotype
B. Chart notes or medical record documenting history of blood cell transfusions for the previous two years

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a hematologist.

IV. CRITERIA FOR INITIAL APPROVAL

Beta-thalassemia
Authorization of 3 months for a one-time administration may be granted when all of the following criteria are met:
A. Member is 4 years of age or older and meets both of the following criteria:
    1. Member weighs at least 6 kg
    2. Member is reasonably anticipated to provide at least the minimum number of cells required to initiate the manufacturing process
B. Member has a diagnosis of transfusion-dependent beta-thalassemia with a non-β0/β0 OR β0/β0 genotype confirmed via genetic testing (Appendix A):
C. Member requires regular blood cell transfusions and meets one of the following criteria within the previous two years:
    1. Member has received at least 100 milliliter per kilogram of packed red blood cells (pRBCs) per year
    2. Member has received at least 8 transfusions events of packed red blood cells (pRBCs) per year
D. Member has not received Zynteglo or any other gene therapy previously
E. Member is not positive for the presence of human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2)

V. APPENDIX

Examples of non-β0/β0 OR β0/β0 genotypes:
1. β0/β0
2. β0/β+
3. βE/β0
4. β0/IVS-I-110
5. IVS-I-110/IVS-1-110

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Zynteglo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2021 Guidelines for the management of transfusion dependent thalassaemia (TDT).

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zynteglo are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VIII. REFERENCES

1. Zynteglo [package insert]. Somerville, MA: Bluebird Bio; August 2022.
2. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non-β0/β0 Genotype β-Thalassemia. N Engl J Med. 2022;386(5):415-427.
3. Ashutosh Lal, Franco Locatelli, Janet L. Kwiatkowski, Andreas E. Kulozik, Evangelia Yannaki, John B. Porter, Isabelle Thuret, Martin G. Sauer, Heidi Elliot, Ying Chen, Richard A. Colvin, Alexis A. Thompson; Northstar-3: Interim Results from a Phase 3 Study Evaluating Lentiglobin Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia and Either a β0 or IVS-I-110 Mutation at Both Alleles of the HBB Gene. Blood 2019; 134 (Supplement_1): 815.
4. Cappellini MD, Farmakis D, Porter J, Taher A. 2021 Guidelines for the management of transfusion dependent thalassaemia (TDT). Nicosia, Cyprus: Thalassaemia International Federation, 2021.

ZYNYZ (retifanlimab-dlwr)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Merkel cell carcinoma
Zynyz is indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

Merkel cell carcinoma (MCC)
Authorization of 12 months may be granted for treatment of metastatic, recurrent locally advanced, or recurrent regional MCC.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted (up to 24 months total) when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen AND
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Zynyz.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Merkel Cell Carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zynyz are covered.

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

VI. REFERENCES

1. Zynyz [package insert]. Wilmington, DE: Incyte Corporation; November 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 15, 2023.