Mass General Brigham
Health Plan

2024 Part B Medical Drugs Medical Necessity Guidelines

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Mass General Brigham Advantage Secure (HMO-POS)
Mass General Brigham Advantage (PPO),
and Mass General Brigham Advantage Premier (PPO)

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Reference number(s)
2423-A

STANDARD MEDICARE PART B MANAGEMENT

ACTEMRA (tocilizumab)
TOFIDENCE (tocilizumab-bavi)
TYENNE (tocilizumab-aazg)

POLICY

I. 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
8. Polymyalgia rheumatica

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. 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.

E. Unicentric Castleman disease
Authorization of 12 months may be granted for treatment of unicentric Castleman disease.

F. Multicentric Castleman disease
Authorization of 12 months may be granted for treatment of multicentric Castleman 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 immunotherapy-related inflammatory arthritis.

I. Acute graft versus host disease
Authorization of 12 months may be granted for treatment of acute graft versus host disease.

J. Thyroid Eye Disease
Authorization of 12 months may be granted for treatment of active Graves' orbitopathy.

K. Polymyalgia rheumatica (PMR)
Authorization of 12 months may be granted for treatment of polymyalgia rheumatica (PMR).

III. CONTINUATION OF THERAPY

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

B. All other indications
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.

IV. SUMMARY OF EVIDENCE

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

1. The prescribing information for Actemra and its biosimilars.
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 and its biosimilars 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
8. Polymyalgia rheumatica

V. 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 tocilizumab 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.

Support for using tocilizumab to treat polymyalgia rheumatica can be found in the National Comprehensive Cancer Network's guideline for 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 polymyalgia rheumatica if unable to taper prednisone or no improvement in symptoms.

VI. 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. Tyenne [package insert]. Lake Zurich, IL: Fresenius Kabi USA LLC; March 2024.
4. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 22, 2024.
5. National Comprehensive Cancer Network. The NCCN Drugs & Biologics Compendium. https://www.nccn.org. Accessed January 22, 2024.
6. 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.
7. 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.
8. 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.

Reference number(s)
4797-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Acthar Gel [package insert]. Bedminster, NJ: Mallinckrodt ARD LLC.; October 2021.
2. DRUGDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado. Available at http://www.micromedexsolutions.com. Accessed May 4, 2023.
3. American Society of Health System Pharmacists. AHFS Drug Information. Bethesda, MD. Electronic Version 2020. http://www.online.lexi.com. Accessed May 4, 2023.
4. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: A U.S. consensus report. *Epilepsia*. 2010:51:2175-2189.
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6. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. *Cochrane Database Syst Rev*. 2013;6:CD001770.
7. Riikonen R. Recent advances in pharmacotherapy of infantile spasms. *CNS Drugs* 2014; 28:279-290.
8. Pavone P, et al. Infantile spasms syndrome, West Syndrome and related phenotypes: what we know in 2013. *Brain & Development* 2014; 739-751.
9. Citterio A, La Mantia L, Ciucci G, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev 4*:CD001331.
10. Thompson AJ, Kennard C, Swash M, et al. Relative efficacy of intravenous methylprednisolone and ACTH in the treatment of acute relapse in MS. *Neurology* 1989; 39:969-971.
11. Berkovich R, Agius MA. Mechanisms of action of ACTH in the management of relapsing forms of multiple sclerosis. *Ther Adv Neurol Disord* 2014; 7(2):83-96.
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14. Bomback AS, Canetta PA, Beck Jr LH, et al. Treatment of resistant glomerular diseases with adrenocorticotropic hormone gel: a prospective trial. *Am J Nephrol* 2012; 36:58-67.
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16. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care & Research* 2012; 64(6):797-808.
17. KDIGO clinical practice guideline for glomerulonephritis. *Kidney International Supplements* 2012; 2(2): 259-274.
18. Tran TH, Hughes GJ, Greenfeld C, et al. Overview of current and alternative therapies for idiopathic membranous nephropathy. *Pharmacotherapy* 2015; 35(4):396-411.
19. Mouterde G, Dernis E, Ruyssen-Witrand A, et al. Indications of glucocorticoids in early arthritis and rheumatoid arthritis: recommendations for clinical practice based on data from the literature and expert opinion. *Joint Bone Spine* 2010; 77:597-603.
20. Levine T. Treating refractory dermatomyositis or polymyositis with adrenocorticotropic hormone gel: a retrospective case series. *Drug Design, Development and Therapy* 2012; 6:133-139.
21. Purified Cortrophin Gel [package insert]. Baudette, MN: ANI Pharmaceuticals, Inc.; January 2022.

Reference number(s)
3416-A

STANDARD MEDICARE PART B MANAGEMENT

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 vasoocclusive 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 vasoocclusive crises
Authorization of 12 months may be granted for use in reducing the frequency of vasoocclusive 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 vasoocclusive crisis within the previous 12 months
B. The member meets either of the following:
    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 vasoocclusive crises, or maintenance of such reduction, since initiating therapy with Adakveo.

IV. REFERENCES

1. Adakveo [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2021.
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.

Reference number(s)
4777-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
6251-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4564-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
5499-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
2477-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
2509-A

STANDARD MEDICARE PART B MANAGEMENT

AVASTIN (bevacizumab)
ALYMSYS (bevacizumab-maly)
MVASI (bevacizumab-awwb)
VEGZELMA (bevacizumab-adcd)
ZIRABEV (bevacizumab-bvzr)
Ocular & Other

POLICY

I. 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
Avastin/Alymsys/Mvasi/Vegzelma/Zirabev does not have FDA-approved non-oncology indications. For oncology indications, please see the Avastin/Alymsys/Mvasi/Vegzelma/Zirabev - Oncology MedB policy.

B. Compendial Uses
1. Diabetic macular edema
2. Neovascular (Wet) age-related macular degeneration
3. Branch retinal vein occlusion with macular edema
4. Central retinal vein occlusion with macular edema
5. Proliferative diabetic retinopathy
6. Choroidal neovascularization
7. Neovascular glaucoma
8. Retinopathy of prematurity
9. Choroidal retinal neovascularization secondary to pathologic myopia
10. Epistaxis due to hereditary hemorrhagic telangiectasia 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. Diabetic macular edema
Authorization of 12 months may be granted for the treatment of diabetic macular edema.

B. Neovascular (Wet) age-related macular degeneration
Authorization of 12 months may be granted for the treatment of neovascular (wet) age-related macular degeneration including polypoidal choroidopathy.

C. Macular edema following retinal vein occlusion
Authorization of 12 months may be granted for the treatment of macular edema following retinal vein occlusion.

D. Proliferative diabetic retinopathy
Authorization of 12 months may be granted for the treatment of proliferative diabetic retinopathy.

E. Choroidal neovascularization
Authorization of 12 months may be granted for the treatment of choroidal neovascularization.

F. Neovascular glaucoma with panretinal photocoagulation
Authorization of 12 months may be granted in conjunction to panretinal photocoagulation for the treatment of neovascular glaucoma.

G. Retinopathy of prematurity
Authorization of 12 months may be granted for the treatment of retinopathy of prematurity.

H. Choroidal retinal neovascularization secondary to pathologic myopia
Authorization of 12 months may be granted for the treatment of choroidal retinal neovascularization secondary to pathologic myopia.

I. Epistaxis due to hereditary hemorrhagic telangiectasia syndrome
Authorization of 12 months may be granted for the treatment of epistaxis due to hereditary hemorrhagic telangiectasia 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 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 Avastin, Alymsys, Mvasi, Vegzelma, and Zirabev. The prescribing information only contains oncology indications.
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. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy.
5. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions.

After reviewing the information in the above resources, the following indications are covered for Avastin, Alymsys, Mvasi, Vegzelma, and Zirbev:

1. Diabetic macular edema
2. Neovascular (Wet) age-related macular degeneration
3. Branch retinal vein occlusion with macular edema
4. Central retinal vein occlusion with macular edema
5. Proliferative diabetic retinopathy
6. Choroidal neovascularization
7. Neovascular glaucoma
8. Retinopathy of prematurity
9. Choroidal retinal neovascularization secondary to pathologic myopia
10. Epistaxis due to hereditary hemorrhagic telangiectasia syndrome

V. EXPLANATION OF RATIONALE

Support for diabetic macular edema can be found in a systematic review and network meta-analysis of 24 randomized trials in 6007 patients with diabetic macular edema, antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) agents (aflibercept, bevacizumab, pegaptanib, ranibizumab) was significantly more effective compared with laser photocoagulation in improving vision at 1 year evaluated with the best-corrected visual acuity. Aflibercept significantly improved the likelihood of a gain of 3+ lines and mean BCVA change compared with ranibizumab and bevacizumab. There was no significant difference in functional outcomes at 1 year comparing ranibizumab and bevacizumab, but reduction in central retinal thickness was better with ranibizumab.
A single-center randomized clinical trial also demonstrated that intravitreal injection of bevacizumab every 6 weeks based on clinical response determined by OCT and visual acuity is superior to macular photocoagulation every 4 months (Michaelides et al, 2010). The authors reported the odds of gaining greater than or equal to 10 ETDRS letters over 12 months were 5.1 times greater in the bevacizumab group than in the laser group (adjusted odds ratio, 5.1; 95 % CI: 1.3 to 19.7; p = 0.019).

Support for neovascular (wet) age-related macular degeneration can be found in a multicenter, single-blind, noninferiority trial conducted by the CATT Research Group. The study randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, P=0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. At 1 year, bevacizumab and

ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study.

Support for branch retinal vein occlusion with macular edema can be found in a study by Russo et al. Thirty eyes of 30 consecutive patients with cystoid macular edema secondary to nonischemic branch retinal vein occlusion were assigned to either GLP group or to intravitreal bevacizumab (IB) group. Complete ophthalmologic examinations were performed just before GLP and IB injection at 1, 3, 6, and 12 months after treatment. Changes in logarithm of minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA), central macular thickness (CMT) shown by optical coherence tomography-3 were evaluated. Baseline BCVA (logMAR) and CMT were, respectively, 0.89 +/- 0.13 and 650 +/- 140 microm for the GLP group, 0.87 +/- 0.16 and 690 +/- 120 microm for the IB group. After the treatment, at 1, 3, 6, and 12 months in the GLP group, BCVA had improved by 0.19, 0.22, 0.21, and 0.20 logMAR, CMT had decreased by 40%, 41.3%, 40.5%, and 42%. In the IB group, BCVA had improved by 0.31, 0.32, 0.30, and 0.31 logMAR and CMT had decreased by 59.5%, 59%, 60%, and 60.3%. The group receiving bevacizumab had better BCVA and lower CMT values at all time points ($P < 0.05$). Intravitreal bevacizumab injection improved BCVA and reduced CMT more than GLP. Intravitreal bevacizumab injection was well tolerated and could be used as primary treatment in patients with cystoid macular edema secondary to perfused branch retinal vein occlusion.

Support for central retinal vein occlusion with macular edema can be found in the SCORE2 randomized clinical trial. Intravitreal bevacizumab was not inferior to aflibercept in mean change in visual acuity letter score (VALS) at 6 months (from 50.4 to 69.3 vs from 50.3 to 69.3) in the randomized SCORE-2 trial in patients with macular edema secondary to central retinal or hemiretinal vein occlusion (N=362). There were also no significant between-group differences at 6 months in the proportion of eyes with a VALS gain of at least 15 (61.3% vs 65.1%), a VALS decrease of at least 15 (1.7% each group) or mean decrease in central subfield thickness (387 vs 425 mcm). A post hoc analysis demonstrated that the likelihood of resolution of macular edema was significantly decreased by 72% with bevacizumab. Bevacizumab was associated with 1 case of endophthalmitis (culture negative) and 2 cases of intraocular pressure (IOP) greater than 35 mmHg. An IOP increase of more than 10 mmHg from baseline occurred in 4.9% of patients with bevacizumab and in 2.2% of patients with aflibercept. Intravitreal interventions included 6 months of bevacizumab 1.25 mg every 4 weeks or aflibercept 2 mg every 4 weeks.
In a 24-week, prospective, randomized, double-blind study (n=60 eyes) of patients with macular edema secondary to central retinal vein occlusion (CRVO), intravitreal injections of bevacizumab statistically significantly improved visual acuity compared with sham (Epstein et al). Patients with CRVO for up to 6 months, best corrected visual acuity (BCVA) of 15 to 65 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent approximately 20/50 to 20/500), and a mean central subfield thickness of 300 micrometers (mcm) or greater were included in the study. Patients (mean age of 70.5 years [range, 52 to 93 years]) were randomized to receive either bevacizumab 1.25 mg/0.05 mL via intravitreal injection (n=30 eyes) via the plans plana or sham (n=30 eyes) injection using a needless syringe pressed to the globe every 6 weeks for 6 months (4 injections). The percentage of patients achieving a 15 or greater ETDRS letter improvement (primary endpoint) was 60% vs 20% (p=0.003) in the bevacizumab and sham arms, respectively. At the 24-week follow-up, visual acuity improved from baseline by a mean of 14.1 ETDRS letters in the bevacizumab arm compared with a mean decrease from baseline of 2 ETDRS letters in the sham arm, with a statistically significant treatment difference occurring from week 12 and beyond (p less than 0.01). There was a statistically significant improvement in the mean decrease in central retinal thickness (CRT; 426 vs 102 mcm), respectively, at all-time points up to week 24 (p less than 0.001). There was no residual edema (CRT less than 300 mcm) at 24 weeks in 86.7% in the bevacizumab arm compared with 20% in the sham arm (p less than 0.001). Iris rubeosis occurred at week 24 in 16.7% of patients in the sham arm and 0% in the bevacizumab arm (p=0.052). There were no reports of serious adverse events, endophthalmitis, or retinal tear or detachment.

Support for proliferative diabetic retinopathy can be found in a study by Mirshahi et al. A prospective, fellow-eye sham controlled clinical trial was conducted on 80 eyes of 40 high-risk characteristic proliferative diabetic retinopathy type II diabetics. All cases received standard laser treatment according to Early Treatment Diabetic Retinopathy Study protocol. Avastin-assigned eyes received 1.25 mg intravitreal bevacizumab on the first session of their laser treatments. Fluorescein angiography was performed at baseline and at weeks 6 and 16, and proliferative diabetic retinopathy regression was evaluated in a masked fashion. The median age was 52 years (range: 39-68) and 30% of the participants were male. All patients were followed for 16 weeks. A total of 87.5% of Avastin-injected eyes and 25% of sham group showed complete regression at week 6 of follow-up ($p<0.005$). However, at week 16, PDR recurred in a sizable number of the Avastin-treated eyes, and the complete regression rate in the two groups became identical (25%; $p=1.000$); partial regression rates were 70% vs 65%. In the subgroup of Avastin-treated eyes, multivariate analysis identified hemoglobin A1c as the strongest predictor of proliferative diabetic retinopathy recurrence ($p=0.033$). Intravitreal bevacizumab remarkably augmented the short-term response to scatter panretinal laser photocoagulation in high-risk characteristic proliferative diabetic retinopathy but the effect was short-lived, as many of the eyes showed rapid recurrence. Alternative dosing (multiple and/or periodic intravitreal Avastin injections) is recommended for further evaluation.

Support for choroidal neovascularization can be found in a study published by Wang et al. Treatment with anti-vascular endothelial growth factor injections was more effective compared with photodynamic therapy, with significant improvements in best corrected visual acuity and retinal thickness reduction. A systematic review identified 2 randomized trials of patients treated with bevacizumab or ranibizumab for myopic choroidal neovascularization (N=32 eyes, duration 6 months; N=48 eyes, duration 18 months), and a meta-analysis found no significant difference between these groups in best corrected visual acuity or retinal thickness reduction. In the 6-month study, the number of required injections did not significantly differ (2.8 vs 2.4); however, in the 18-month study, significantly more injections were required in the bevacizumab group compared with ranibizumab (4.7 vs 2.6).
Chan and colleagues conducted a prospective pilot study studying the 1-year results of intravitreal bevacizumab for myopic choroidal neovascularization. Twenty-nine eyes of 29 patients with myopic CNV were prospectively recruited to receive three initial monthly intravitreal bevacizumab injections. Three additional monthly injections were performed in eyes with persistent or recurrent CNV after 3 months. The mean spherical equivalent refractive error was -10.0 D. Sixteen eyes had previous photodynamic therapy (PDT) and 13 eyes had no prior PDT. All patients completed follow-up at 1 year. Following the initial three bevacizumab injections, 27 (93.1%) eyes had angiographic closure and two (6.9%) required further treatment. Two additional patients required re-treatment for CNV recurrence between 6 and 9 months. The mean baseline logarithm of the minimum angle of resolution (logMAR best-corrected visual acuity) was 0.62 (20/83), which improved to 0.38 (20/48) at 12 months ($p<0.001$). The mean visual improvement was 2.4 lines and 21 (72.4%) eyes had improvement of > or =2 lines. Optical coherence tomography showed significant reduction in central foveal thickness following treatment. Eyes without previous PDT were more likely to gain > or =2 lines after treatment than eyes that had previous PDT ($p = 0.010$). The 1-year outcomes confirmed the results of previous short-term studies that intravitreal bevacizumab is effective for myopic CNV, with a high proportion of patients sustaining visual gain after treatment.

Support for neovascular glaucoma can be found in a study by Yazdani et al. This randomized controlled trial included 26 eyes of 26 patients with neovascular glaucoma (NVG). All eyes received conventional treatment for NVG and were randomly allocated to three 2.5 mg intravitreal bevacizumab injections at 4-week intervals or a sham procedure (subconjunctival normal saline) at similar time intervals and in the same setting. Overall, 14 eyes of 14 patients received intravitral bevacizumab and 12 eyes of 12 subjects were allocated to the sham procedure and followed for a mean period of 5.9+/-1.4 months. The intravitreal bevacizumab group demonstrated significant reduction in intraocular pressure from a baseline value of 33.4+/-14.5 mm Hg to

21.8+/-13.7 mm Hg (P=0.007), 25.1+/-20 mm Hg (P=0.058), and 23.9+/-18.7 mm Hg (P=0.047) at 1, 3, and 6 months after intervention, respectively. Iris neovascularization was also significantly reduced from a mean baseline value of 347+/-48 degrees to 206+/-185 degrees (P=0.01), 180+/-187 degrees (P=0.004), and 180+/-180 degrees (P=0.004) at 1, 3, and 6 months after intervention. In contrast, intraocular pressure and iris neovascularization remained unchanged or increased insignificantly at all follow-up intervals in the control group. No significant change in visual acuity was observed within the study groups at any time interval. The study groups were comparable in terms of requirement for additional interventions such as panretinal photocoagulation and cyclodestructive procedures.

Support for retinopathy of prematurity can be found in a study by the BEAT-ROP Cooperative Group. The BEAT-ROP Cooperative Group conducted a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) retinopathy of prematurity. Infants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. One hundred and fifty infants were enrolled (total sample of 300 eyes); 143 infants survived to 54 weeks' postmenstrual age, and the 7 infants who died were not included in the primary-outcome analyses. Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], P=0.002). A significant treatment effect was found for zone I retinopathy of prematurity (P=0.003) but not for zone II disease (P=0.27). Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina. This trial was too small to assess safety.

Support for choroidal retinal neovascularization secondary to pathologic myopia can be found in a systematic review by Wang and Chen. Treatment with anti-vascular endothelial growth factor injections was more effective compared with photodynamic therapy, with significant improvements in best corrected visual acuity and retinal thickness reduction. A systematic review identified 2 randomized trials of patients treated with bevacizumab or ranibizumab for myopic choroidal neovascularization (N=32 eyes, duration 6 months; N=48 eyes, duration 18 months), and a meta-analysis found no significant difference between these groups in best corrected visual acuity or retinal thickness reduction. In the 6-month study, the number of required injections did not significantly differ (2.8 vs 2.4); however, in the 18-month study, significantly more injections were required in the bevacizumab group compared with ranibizumab (4.7 vs 2.6).

Support for using bevacizumab as an intranasal injection to treat epistaxis due to hereditary hemorrhagic telangiectasia syndrome can be found in two studies. Steineger and colleagues found repeated intranasal submucosal bevacizumab injections produced a continued positive response in 36.3% of patients with hereditary hemorrhagic telangiectasia in a single arm study (N=33). The mean duration from first to last injection in responders was 54 months (range, 33 to 66 months). A positive response was any reduction in the epistaxis severity score (ESS) and epistaxis intensity, frequency, and need for blood transfusion (IFT) score 6 to 8 weeks after the procedure. After the first intranasal bevacizumab procedure, 87.8% of patients had a positive response. With repeated injections, 33% of patients had a gradual shortening of the effect duration that resulted in treatment discontinuation when the effect duration was less than 8 weeks. Included patients had no benefit from repeated pulsed-dye laser, diode laser, argon plasma coagulation, and septodermoplasty in the previous 2 years or had contraindications to those therapies. During the 5.5 years of study observation, no local adverse events were reported. However, there was 1 case of bilateral osteonecrosis of the knees after eight 200-mg doses with a mean interval between treatments of 5.6 months. The bevacizumab dosage was 100 mg per procedure (50 mg in each side of the nose) initially and later increased to 200 mg per procedure (100 mg on each side). Injections were in the sphenopalatine area, upper part of the bony septum, upper part

of the lateral nasal wall, and the anterior floor of the nose; injections were repeated as soon as the effect of the previous treatment diminished. The mean duration between injections was 5.1 +/- 2 months (range, 7 weeks to 11 months).

A prospective study by Karnezis et al found submucosal bevacizumab injection plus nasal spray significantly decreased epistaxis severity scores (ESS) over a 9- to 12-month follow-up period in patients with recalcitrant hereditary hemorrhagic telangiectasia epistaxis. Patients (n=19, mean age, 60 years) received an intranasal submucosal injection of bevacizumab 100 mg (25 mg/mL) at initial presentation. Injections were made along the lateral nasal wall, middle/inferior turbinates, nasal floor, and bony septum; there was intention for two-thirds of the injection to be placed in the anterior one-third of the nose. Over the 12-month follow-up, 6 of the 19 patients received 8 additional treatments with bevacizumab 100 mg nasal spray via a metered dose atomizer, which was given 3, 4, 6, 7, and 11 months after the original submucosal injection for increased bleeding. Following the submucosal injection, the ESS score significantly improved from a mean of 8.12 (severe disease) before treatment to a nadir of 2 (mild disease) at 2 months; in evaluable patients at month 11, the maximum mean ESS was 3.6.

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2746-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

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Reference number(s)
2502-A

STANDARD MEDICARE PART B MANAGEMENT

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, 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.

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 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. Active 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. 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. Kidney Disease: Improving Global Outcomes (KDIGO) 2024 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 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. 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. 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.

According to the 2023 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. Hydroxychloroquine is recommended for all patients, unless contraindicated. Glucocorticoids (GC), if needed, can be used at doses and route of administration that depend on the type and severity of organ involvement and should be reduced to maintenance dose of less than or equal to 5 mg/day (prednisone equivalent). In patients not responding to hydroxychloroquine (alone or in combination with GC) or patients unable to reduce GC below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as methotrexate, azathioprine, or mycophenolate and/or biological agents (e.g., belimumab or anifrolumab) should be considered. In patients with organ-threatening or life-threatening disease, cyclophosphamide should be considered.

VIII. REFERENCES

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Reference number(s)
3348-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

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Reference number(s)
2624-A

STANDARD MEDICARE PART B MANAGEMENT

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**[7]
    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 24 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. REFERENCES

1. Botox [package insert]. Irvine, CA: Allergan, Inc.; August 2023.
2. DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado. Available at http://www.micromedexsolutions.com. Accessed August 1, 2023.
3. AHFS Drug Information. Available at http://online.lexi.com/lcom. Accessed August 1, 2023.
4. Dysport [package insert]. Wrexham, UK: Ipsen Biopharm, Ltd.; July 2020.
5. Xeomin [package insert]. Dessau-Rosslau, Germany: Merz Pharmaceuticals, LLC. April 2021.
6. Myobloc [package insert]. South San Francisco, CA: Solstice Neurosciences, Inc.; March 2021.
7. Daxxify [package insert]. Newark, CA: Revance, Therapeutics Inc.; August 2023.

Reference number(s)
5738-A

STANDARD MEDICARE PART B MANAGEMENT

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 Indication
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. REFERENCES

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

Reference number(s)
4703-A

STANDARD MEDICARE PART B MANAGEMENT

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.

VII. REFERENCES

1. Cimzia [package insert]. Smyrna, GA: UCB, Inc.; December 2022.
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.
3. 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.
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5. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59(6):762-784.
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8. Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis.* 2005;64(Suppl II):ii14–ii17.
9. Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol.* 2022;18(8):465-479.

10. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis.* 2011;70:896–904.
11. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomized placebo-controlled Phase 3 study. *Ann Rheum Dis.* 2014;73(1):39-47.
12. 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.
13. 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.
14. 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.
15. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2019;80(4):1029-1072.
16. Utilization Management (UM) Criteria Review CVS Caremark P&T Subgroup. Gastroenterology – IBD Agents – UM Criteria. December 2018.
17. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol*. 2019;71(1):5-32. Doi:10.1002/art.40726.
18. Menter A, Cordero KM, Davis DM, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol.* 2020;82(1):161-201.
19. 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): 1445-86.
20. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-81.
21. Clinical Consult: CVS Caremark Clinical Programs Review. Focus on Rheumatology Clinical Programs. March 2021.
22. Smolen JS, Aletaha D. Assessment of rheumatoid arthritis activity in clinical trials and clinical practice. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Available with subscription. URL: www.uptodate.com. Accessed March 19, 2021.
23. Feuerstein J, Ho E, 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.
24. Elmets C, Korman N, et al. Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapy and Alternative Medicine Modalities for Psoriasis Severity Measures. *J Am Acad Dermatol.* 2021; 84:432-470.
25. 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.
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.

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Reference number(s)
4703-A

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Reviewed:	CDPR / DNC 05/2021, SNG 08/2021, APN 08/2022, SKY 12/2022, APN 01/2023, APN 08/2023, AN 10/2023
External Review:	Dermatology: 10/2021, 10/2022, 10/2023 Rheumatology: 10/2021, 11/2022, 11/2023 Gastroenterology: 11/2021, 12/2022, 05/2023, 09/2023

Reference number(s)
2065-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
2189-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Cinryze [package insert]. Lexington, MA: ViroPharma Biologics; February 2023.
2. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed April 17, 2020.
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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.

Reference number(s)
4849-A

STANDARD MEDICARE PART B MANAGEMENT

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 and moderate hereditary Factor X deficiency.

Limitation of Use:
Perioperative management of bleeding in major surgery in patients with severe hereditary Factor X deficiency has not been studied.

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 or moderate hereditary Factor X deficiency (i.e., baseline Factor X assay level ≥ 1 %).

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. REFERENCES

1. Coagadex [package insert]. Durham, NC: Bio Products Laboratory USA, Inc.; November 2020.
2. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised April 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed September 26, 2022.
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Reference number(s)
6023-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.
   .

Reference number(s)
4851-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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 other bleeding disorders. Revised April 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed September 26, 2022.

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 March 28, 2022. Available with subscription. URL: http://online.lexi.com/lco. Accessed September 26, 2022.

Reference number(s)
4548-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number
6360-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4234-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Crysvita [package insert]. Bedminster, NJ: Kyowa Kirin, Inc.; June 2020.
2. NIH. U.S. National Library of Medicine. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT02163577. Accessed October 24, 2018.
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

Reference number(s)
5671-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
5935-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
6121-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4739-A

STANDARD MEDICARE PART B MANAGEMENT

EMPAVELI (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 Indications
Empaveli is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

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: flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency.
B. For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

III. CRITERIA FOR INITIAL APPROVAL

Paroxysmal nocturnal hemoglobinuria
Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:

A. The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) as demonstrated by either of the following:
    1. At least 5% PNH cells
    2. At least 51% of GPI-AP deficient poly-morphonuclear cells
B. Flow cytometry is used to demonstrate GPI-APs deficiency

IV. CONTINUATION OF THERAPY

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

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

A. The member is currently receiving therapy with Empaveli
B. The member is receiving benefit from therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels)

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. REFERENCES

1. Empaveli [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; May 2021.
2. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. *Hematology.* 2011; 21-29.
3. 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.
4. Preis M, Lowrey CH. Laboratory tests for paroxysmal nocturnal hemoglobinuria (PNH). Am J Hematol. 2014;89(3):339-341.
5. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.

Reference number
2666-A

STANDARD MEDICARE PART B MANAGEMENT

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

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Reference number(s)
6003-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
4820-A

STANDARD MEDICARE PART B MANAGEMENT

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

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3. epoprostenol for Injection [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; January 2021.

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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.
12. External Infusion Pumps- Policy Article (A52507) Version R31. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed October 2, 2023.

Reference number
2920-A

STANDARD MEDICARE PART B MANAGEMENT

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

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):dgaa048. doi:10.1210/clinem/dgaa048
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Reference number(s)
4233-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.
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Reference number(s)
2507-A

STANDARD MEDICARE PART B MANAGEMENT

EYLEA (aflibercept)
EYLEA HD (aflibercept)
OPUVIZ (aflibercept-yszy)
YESAFILI (aflibercept-jbvf)
AHZANTIVE (aflibercept-mrbb)

POLICY

I. 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

Ahzantive, Opuviz and Yesafili are indicated for the treatment of:
A. Diabetic macular edema
B. Diabetic retinopathy
C. Neovascular (wet) age-related macular degeneration
D. 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
Authorization of 12 months may be granted for treatment of diabetic macular edema.

B. Diabetic Retinopathy
Authorization of 12 months may be granted for treatment of diabetic retinopathy.

C. Neovascular (Wet) Age-Related Macular Degeneration
Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

D. Macular Edema Following Retinal Vein Occlusion (Eylea and Biosimilars Only)
Authorization of 12 months may be granted for treatment of macular edema following retinal vein occlusion.

E. Retinopathy of Prematurity (Eylea and Biosimilars Only)
Authorization of 12 months may be granted for 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 medication.
B. The requested medication is being used to treat an indication enumerated in Section II.
C. 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 Eylea, Eylea HD, Ahzantive, Opuviz, and Yesafili.
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 Occlusions.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Eylea, Eylea HD, Ahzantive, Opuviz and Yesafili 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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Reference number(s)
4852-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Alprolix [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; October 2020.
2. BeneFIX [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; November 2022.
3. Ixinity [package insert]. Chicago, IL: Medexus Pharma, Inc.; May 2022.
4. Rixubis [package insert]. Lexington, MA: Baxalta US Inc.; June 2020.
5. AlphaNine SD [package insert]. Los Angeles, CA: Grifols Biologicals LLC; March 2021.
6. Idelvion [package insert]. Kankakee, IL: CSL Behring LLC; July 2021.

7. Rebinyn [package insert]. DK-2880 Bagsvaerd, Denmark: Novo Nordisk A/S; August 2022.
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Reference number(s)
4848-A

STANDARD MEDICARE PART B MANAGEMENT

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. Drug toxicity, anticoagulant

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. REFERENCES

1. Profilnine [package insert]. Los Angeles, CA: Grifols Biologicals LLC; March 2021.
2. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically www.micromedexsolutions.com [available with subscription]. Accessed December 2, 2022.
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Reference number(s)
4932-A

STANDARD MEDICARE PART B MANAGEMENT

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

B. Age < 2 years
C. Pregnancy
D. Fluid/electrolyte imbalance
E. High risk for cardiovascular or cerebrovascular disease (especially the elderly)
F. Predisposition to thrombus formation
G. Trauma requiring surgery
H. Life-threatening bleed
I. Contraindication or intolerance to desmopressin
J. Severe type 1 von Willebrand disease
K. Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

IV. REFERENCES

1. Advate [package insert]. Lexington, MA: Baxalta US Inc.; December 2018.
2. Jivi [package insert]. Whippany, NJ: Bayer HealthCare LLC; August 2018.
3. Kogenate FS [package insert]. Whippany, NJ: Bayer HealthCare LLC; May 2016.
4. Kogenate FS with BIO-SET [package insert]. Whippany, NJ: Bayer HealthCare LLC; May 2016.
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6. Kovaltry [package insert]. Whippany, NJ: Bayer Healthcare LLC; December 2022.
7. Novoeight [package insert]. Plainsboro, NJ: Novo Nordisk Inc., July 2020.
8. Nuwiq [package insert]. Hoboken, NJ: Octapharma USA, Inc., June 2021.
9. Recombinate with 5 mL Sterile Water for Injection using BAXAJECT II [package insert]. Lexington, MA: Baxalta US Inc.; June 2018.
10. Xyntha [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; July 2022.
11. Xyntha Solufuse [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; July 2022.
12. Adynovate [package insert]. Lexington, MA: Baxalta US Inc.; July 2021.
13. Afstyla [package insert]. Marburg, Germany: CSL Behring GmbH. April 2021.
14. Eloctate [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; December 2020.
15. Hemofil M [package insert]. Lexington, MA: Baxalta US Inc.; June 2018.
16. Alphanate [package insert]. Los Angeles, CA: Grifols Biologicals Inc.; March 2021.
17. Humate-P [package insert]. Marburg, Germany: CSL Behring GmbH; June 2020.
18. Koate [package insert]. Research Triangle Park, NC: Grifols Therapeutics Inc.; June 2018.
19. Koate-DVI [package insert]. Research Triangle Park, NC: Grifols Therapeutics Inc.; August 2012.

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22. Tiede A, Rand J, Budde U, et al. How I treat the acquired von Willebrand syndrome. *Blood*. 2011;117(25):6777-85.
23. 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.
24. 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.
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26. 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 December 1, 2022.
27. Acquired hemophilia. World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1186.pdf. Accessed December 1, 2022.
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33. Reding MT, NG HJ, Poulsen LH, et al. Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII. *Journal of thrombosis and Haemostasis*. 2017; 15: 411-9.
34. Esperoct [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; August 2022.
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Reference number(s)
2419-A

STANDARD MEDICARE PART B MANAGEMENT

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

1. Fasenra [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; April 2024.

2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023 update. Available at: https://ginasthma.org/wp-content/uploads/2023/07/GINA-Full-Report-23_07_06-WMS.pdf. Accessed March 8, 2024.
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Reference number(s)
4800-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. FEIBA [package insert]. Lexington, MA: Baxalta US Inc.; February 2020.
2. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/988283 [available with subscription]. Accessed December 3, 2022.
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Reference number(s)
3361-A

STANDARD MEDICARE PART B MANAGEMENT

FORTEO (teriparatide)
TERIPARATIDE (branded generic)
teriparatide

POLICY

I. 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. Treatment of postmenopausal women with osteoporosis at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy.
2. Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.
3. Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or who have failed or are intolerant to other available osteoporosis 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

A. Osteoporosis treatment
Authorization of 12 months may be granted for the treatment of osteoporosis in men or postmenopausal women at high risk for fracture.

B. Glucocorticoid-induced osteoporosis
Authorization of 12 months may be granted for the treatment of glucocorticoid-induced 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 of 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.

IV. OTHER

The cumulative duration of parathyroid hormone analogs (teriparatide and abaloparatide) will not exceed a total of 24 months in the member's lifetime unless the member remains at or has returned to having a high risk for fracture.

V. SUMMARY OF EVIDENCE

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

1. The prescribing information for Forteo and teriparatide.
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 Forteo and teriparatide are covered.

VI. EXPLANATION OF RATIONALE

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

VII. REFERENCES

1. Forteo [package insert]. Indianapolis, IN: Eli Lilly and Company; July 2024.
2. Teriparatide [package insert]. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; November 2021.
3. Teriparatide [package insert]. Morristown, NJ: Alvogen, Inc.; November 2023.
4. Teriparatide [package insert]. Weston, FL: Apotex Corp.; December 2023.

Reference number(s)
4235-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; January 2022.

Reference number(s)
4798-A

STANDARD MEDICARE PART B MANAGEMENT

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

For initial and continuation requests, dosing does not exceed the following:
A. Induction: 3mg/kg subcutaneously once weekly for the first 4 weeks.
B. Maintenance: 1.5mg/kg once weekly, or 3mg/kg once every 2 weeks, or 6mg/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. REFERENCES

1. Hemlibra [package insert]. South San Francisco, CA: Genentech, Inc.; June 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 other bleeding disorders. Revised March 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed December 3, 2022.

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 3, 2022.
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 3, 2022.
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.

Reference number(s)
2474-A

STANDARD MEDICARE PART B MANAGEMENT

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

Reference number(s)
4615-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
2478-A

STANDARD MEDICARE PART B MANAGEMENT

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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Reference number(s)
2479-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4697-A

STANDARD MEDICARE PART B MANAGEMENT

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

1. Ilumya [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; December 2022.
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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.

Reference number(s)
5656-A

STANDARD MEDICARE PART B MANAGEMENT

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

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Reference number
1979-A

STANDARD MEDICARE PART B MANAGEMENT

REMICADE (infliximab)
AVSOLA (infliximab-axxq)
INFLECTRA (infliximab-dyyb)
RENFLEXIS (infliximab-abda)
ZYMFENTRA (infliximab-dyyb)
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.

2. Zymfentra
   i. Maintenance treatment of moderately to severely active ulcerative colitis in adults following treatment with an infliximab product administered intravenously
   ii. Maintenance treatment of moderately to severely active Crohn's disease in adults following treatment with an infliximab product administered intravenously

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) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
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) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

E. Psoriatic arthritis (PsA) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

F. Plaque psoriasis (PsO) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of plaque psoriasis.

G. Adult-onset Still's disease (AOSD) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of active adult-onset Still's disease.

H. Arthritis in Crohn's disease (CD) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of arthritis in a member with Crohn's disease.

I. Behcet's disease (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of Behcet's disease.

J. Gastrointestinal tract transplantation organ rejection (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 6 months may be granted for treatment of gastrointestinal tract transplantation organ rejection.

K. Giant cell arteritis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 3 months may be granted for treatment of giant cell arteritis.

L. Acute graft versus host disease (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of acute graft versus host disease.

M. Hidradenitis suppurativa (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of hidradenitis suppurativa.

N. Juvenile idiopathic arthritis (JIA) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of active juvenile idiopathic arthritis.

O. Kawasaki disease (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 1 month may be granted for treatment of Kawasaki disease.

P. Necrobiosis lipoidica diabeticorum (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of necrobiosis lipoidica diabeticorum.

Q. Polyarteritis nodosa (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of polyarteritis nodosa.

R. Pyoderma gangrenosum (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of pyoderma gangrenosum.

S. SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of severe, refractory SAPHO syndrome.

T. Sarcoidosis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of sarcoidosis.

U. Subcorneal pustular dermatosis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 6 months may be granted for treatment of subcorneal pustular dermatosis.

V. Synovitis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of synovitis.

W. Takayasu's arteritis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of Takayasu's arteritis.

X. Uveitis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of uveitis.

Y. Immune checkpoint inhibitor-related inflammatory arthritis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 12 months may be granted for treatment of immune checkpoint inhibitor-related inflammatory arthritis.

Z. Immune checkpoint inhibitor-related toxicity (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity.

AA. Multisystem inflammatory syndrome in children (MIS-C) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
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, Renflexis, or Zymfentra.
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) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

C. All other indications (Avsola/Inflectra/infliximab/Remicade/Renflexis only)
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, and its biosimilars.
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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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, and its biosimilars (excluding Zymfentra) 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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Reference number(s)
6106-A

STANDARD MEDICARE PART B MANAGEMENT

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

Reference number(s)
6146-A

STANDARD MEDICARE PART B MANAGEMENT

JESDUVROQ (daprodustat)

POLICY

I. 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
Jesduvroq is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least four months.

Limitations of Use:
A. Jesduvroq has not been shown to improve quality of life, fatigue, or patient well-being.
B. Jesduvroq is not indicated for use:
    1. As a substitute for red blood cell transfusions in patients who require immediate correction of anemia.
    2. For treatment of anemia of chronic kidney disease in patients who are not on dialysis.

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 pretreatment hemoglobin level exclude values due to a 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 receiving dialysis for at least 4 months with a pretreatment hemoglobin of less than or equal to 11 g/dL.

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 weeks may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Jesduvroq.
2. Jesduvroq is being used to treat anemia due to chronic kidney disease (CKD) in adult members receiving dialysis.
3. Jesduvroq 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 Jesduvroq.
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 Jesduvroq are covered.

V. EXPLANATION OF RATIONALE

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

VI. REFERENCES

1. Jesduvroq [package insert]. Durham, NC: GlaxoSmithKline; July 2023.
2. Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. *N Engl J Med*. 2021;385(25):2325-2335.

Reference number(s)
6559-A

STANDARD MEDICARE PART B MANAGEMENT

KISUNLA (donanemab-azbt)

POLICY

I. 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
Kisunla is indicated for the treatment of Alzheimer's disease. Treatment with Kisunla should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the 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 7 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 Kisunla.
B. Kisunla 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 Kisunla.
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 Kisunla are covered.

VII. EXPLANATION OF RATIONALE

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

Using Kisunla 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.

Support for using a lumbar puncture to confirm amyloid pathology in cerebrospinal fluid can be found in an article published by Schindler et al. Decreases in cerebrospinal fluid (CSF) Aβ42 levels and increases in CSF total Tau (tTau) and phosphorylated Tau-181 (pTau) may be the earliest markers of AD brain pathology. The ratio of Aβ42 with another AD biomarker (e.g. tTau/Aβ42, pTau/Aβ42, or Aβ42/Aβ40) may provide the best correlation with amyloid PET measures.

VIII. REFERENCES

1. Kisunla [package insert]. Indianapolis, IN: Eli Lilly and Company; July 2024.
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, 2024.
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. Centers for Medicare and Medicaid Services. Fact Sheet. June 22, 2023. Accessed July 8, 2024. https://www.cms.gov/files/document/fact-sheet-june-2023.pdf
6. Elecsys Phospho-Tau (181P) CSF 2022-12.

Reference number(s)
5788-A

STANDARD MEDICARE PART B MANAGEMENT

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 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-CNS manifestations of alpha-mannosidosis when the diagnosis is confirmed by a documented deficiency of alpha-mannosidase 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 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. REFERENCES

1. Lamzede [package insert]. Cary, NC: Chiesi USA Inc.; February 2023.

Reference number(s)
5735-A

STANDARD MEDICARE PART B MANAGEMENT

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.
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. Centers for Medicare and Medicaid Services. Fact Sheet. June 22, 2023. Accessed July 11, 2023. https://www.cms.gov/files/document/fact-sheet-june-2023.pdf
6. Elecsys Phospho-Tau (181P) CSF 2022-12.

Reference number(s)
5120-A

STANDARD MEDICARE PART B MANAGEMENT

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. Initial requests:
   1. With clinical atherosclerotic cardiovascular disease (ASCVD): Chart notes confirming clinical ASCVD (see Appendix A).
   2. Without ASCVD: Untreated (before any lipid lowering therapy) LDL-C level.
B. Both initial and continuation requests:
   1. LDL-C level must be dated within six months preceding the authorization request.
   2. If member has contraindication or intolerance to statins, chart notes or medical documentation confirming the contraindication or intolerance (see Appendix B).

III. CRITERIA FOR INITIAL APPROVAL

Primary hyperlipidemia including heterozygous familial hypercholesterolemia (HeFH)
Authorization of 12 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 either of the following criteria:
      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).

3. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (see Appendix B).

B. Member meets all of the following criteria:
   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 either of the following criteria:
      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).
   3. Member will continue to receive concomitant statin therapy if no contraindication or intolerance (see Appendix B).

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).

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 ≥ 300

APPENDIX B. Contraindications to statin therapy
- Score of 7 or higher on the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) and failed statin rechallenge
- Presence of statin-associated muscle symptoms with elevation in creatine kinase (CK) level > 3 times upper limit of normal (ULN)
- Statin-associated elevation in creatine kinase (CK) level ≥ 10 times ULN

- 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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Reference number(s)
4458-A

STANDARD MEDICARE PART B MANAGEMENT

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 x 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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Reference number(s)
4212-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Fusilev [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; November 2020.
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Reference number(s)
6238-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
2508-A

STANDARD MEDICARE PART B MANAGEMENT

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.

VI. REFERENCE

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Reference number(s)
5713-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
2304-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4237-A

STANDARD MEDICARE PART B MANAGEMENT

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

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.

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 be receiving chemotherapy and radiation therapy at the same time.

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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2. Fulphila [package insert]. Morgantown, WV: Mylan Pharmaceuticals, Inc; October 2021.
3. Udenyca [package insert]. Redwood City, CA: Coherus BioSciences, Inc; June 2021.
4. Ziextenzo [package insert]. Princeton, NJ: Sandoz Inc.; March 2021.
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7. Stimufend [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC; September 2022.
8. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed May 18, 2022.

9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf Accessed May 18, 2022.
10. IBM Micromedex® DRUGDEX ® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com (Accessed: May 18, 2022).
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hairy Cell Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf Accessed May 18, 2022.
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13. Fruehauf S, Klaus J, Huesing J, et al: Efficient mobilization of peripheral blood stem cells following CAD chemotherapy and a single dose of pegylated G-CSF in patients with multiple myeloma. Bone Marrow Transplantation 2007; 39(12):743-750.

Reference number(s)
4758-A

STANDARD MEDICARE PART B MANAGEMENT

NEUPOGEN (filgrastim)
GRANIX (tbo-filgrastim)
NIVESTYM (filgrastim-aafi)
RELEUKO (filgrastim-ayow)
ZARXIO (filgrastim-sndz)

POLICY

I. 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

Neupogen

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
   Neupogen 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 significant incidence of severe neutropenia with fever.

2. Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
   Neupogen is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

3. Patients with Cancer Undergoing Bone Marrow Transplantation
   Neupogen is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.

4. Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
   Neupogen is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

5. Patients with Severe Chronic Neutropenia
   Neupogen is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

6. Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
   Neupogen is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

Nivestym

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy

Nivestym 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 significant incidence of severe neutropenia with fever.

2. Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
   Nivestym is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

3. Patients with Cancer Undergoing Bone Marrow Transplantation (BMT)
   Nivestym is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

4. Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
   Nivestym is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

5. Patients with Severe Chronic Neutropenia
   Nivestym is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Granix
Granix is indicated to reduce the duration of severe neutropenia in adult and pediatric patients 1 month and older with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Zarxio
1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
   Zarxio 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 significant incidence of severe neutropenia with fever.

2. Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
   Zarxio is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML).

3. Patients with Cancer Undergoing Bone Marrow Transplantation
   Zarxio is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

4. Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
   Zarxio is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

5. Patients with Severe Chronic Neutropenia
   Zarxio is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Releuko
1. Patients with Cancer Receiving Myelosuppressive Chemotherapy

Releuko 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 significant incidence of severe neutropenia with fever.

2. Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
   Releuko is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

3. Patients with Cancer Undergoing Bone Marrow Transplantation
   Releuko is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia), in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

4. Patients with Severe Chronic Neutropenia
   Releuko is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

B. Compendial Uses
   1. Treatment of chemotherapy-induced febrile neutropenia
   2. Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
   3. Treatment of anemia and neutropenia in patients with myelodysplastic syndromes (MDS)
   4. Stem cell transplantation-related indications
   5. Agranulocytosis (non-chemotherapy drug induced)
   6. Aplastic anemia
   7. Neutropenia related to human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS)
   8. Neutropenia related to renal transplantation
   9. Acute myeloid leukemia
   10. Supportive care for neutropenic patients with CAR T-cell-related toxicities
   11. Hairy Cell Leukemia, neutropenic fever
   12. Chronic Myeloid Leukemia, treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
   13. Glycogen Storage Disease (GSD) Type 1
   14. Reducing the instance of neonatal sepsis in infants with preeclampsia-associated neutropenia
   15. Perioperative administration of filgrastim to patients with esophageal cancer undergoing esophagectomy reduced infectious complications following surgery
   16. Improving the neutrophil count in Shwachman 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 febrile neutropenia, submit 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 x 10^9/L) neutropenia
      g. Prior episodes of febrile neutropenia

B. Other indications

Authorization of 6 months may be granted for members with any of the following indications:

1. Myelodysplastic syndrome (anemia or neutropenia)
2. Stem cell transplantation-related indications (including applicable gene therapy protocols)
3. Agranulocytosis (non-chemotherapy drug induced)
4. Aplastic anemia
5. Neutropenia related to HIV/AIDS
6. Neutropenia related to renal transplantation
7. Acute myeloid leukemia
8. Severe chronic neutropenia (congenital, cyclic, or idiopathic)
9. Hematopoietic Subsyndrome of Acute Radiation Syndrome
   Treatment for radiation-induced myelosuppression following a radiological/nuclear incident
10. CAR T-cell-related toxicities
    Supportive care for neutropenic patients with CAR T-cell-related toxicities
11. Hairy Cell Leukemia
    Members with hairy cell leukemia with neutropenic fever following chemotherapy
12. Chronic Myeloid Leukemia
    Members with chronic myeloid leukemia (CML) for treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
13. Glycogen Storage Disease (GSD) Type 1
    Individuals with GSD Type 1 for treatment of low neutrophil counts
14. Reducing the instance of neonatal sepsis in infants with preeclampsia-associated neutropenia
15. Perioperative administration of filgrastim to patients with esophageal cancer undergoing esophagectomy to reduce infectious complications following surgery
16. Improving the neutrophil count in Shwachman 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.

A. Authorization for 6 months may be granted for the treatment of chronic myeloid leukemia 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
    ii. No evidence of disease progression while on the current regimen

B. 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 Neupogen, Granix, Nivestym, Releuko, and Zarxio.
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: Myelodysplastic syndromes
4. NCCN Guideline: Hematopoietic growth factors
5. NCCN Guideline: Hematopoietic cell transplantation
6. NCCN Guideline: Management of immunotherapy-related toxicities
7. NCCN Guideline: Acute myeloid leukemia
8. NCCN Guideline: Hairy cell leukemia
9. NCCN Guideline: Chronic myeloid leukemia
10. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics
11. 2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors.
12. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Practice Guideline Update
13. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline
14. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Neupogen, Granix, Nivestym, Releuko, and Zarxio are covered in addition to the following:

1. Treatment of chemotherapy-induced febrile neutropenia
2. Prophylaxis for chemotherapy- induced febrile neutropenia in patients with solid tumors
3. Treatment of anemia and neutropenia in patients with myelodysplastic syndromes (MDS)
4. Stem cell transplantation-related indications
5. Agranulocytosis (non-chemotherapy drug induced)
6. Aplastic anemia
7. Neutropenia related to human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS)
8. Neutropenia related to renal transplantation
9. Acute myeloid leukemia
10. Supporting care for neutropenic patients with CAR T-cell-related toxicities
11. Hairy cell leukemia, neutropenic fever
12. Chronic myeloid leukemia, treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy

13. Glycogen storage disease type I
14. Reducing the instance of neonatal sepsis in infants with preeclampsia-associated neutropenia
15. Perioperative administration of filgrastim to patients with esophageal cancer undergoing esophagectomy reduced infectious complications following surgery
16. Improving neutrophil count in Shwachman syndrome

VI. EXPLANATION OF RATIONALE

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

Support for using filgrastim to treat anemia and neutropenia in patients with myelodysplastic syndromes can be found in the National Comprehensive Cancer Network's guideline for myelodysplastic syndromes. The NCCN Guideline for myelodysplastic syndromes supports the use of filgrastim as treatment of lower risk (IPSS-R very low, low, intermediate) disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts greater than or equal to 15% (or ring sideroblasts greater than or equal to 5% with an SF3B1 mutation), with serum erythropoietin less than or equal to 500 mU/mL in combination with an erythropoiesis-stimulating agent (ESA). The guideline also supports using filgrastim to treat lower risk disease as previously described following no response (despite adequate iron stores) or erythroid response followed by loss of response to an ESA alone.

Support for using filgrastim as prophylaxis against febrile neutropenia in patients receiving chemotherapy for solid tumors and 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 filgrastim as prophylaxis of chemotherapy-induced febrile neutropenia or other dose limiting neutropenic events in high-risk (greater than 20% overall risk of febrile neutropenia) in patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings.
The guideline also supports using filgrastim for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors. Consider using filgrastim for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in low-risk (<10% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have 2 or more patient-related risk factors. Use of granulocyte colony-stimulating factors in this setting is based on clinical judgment.

Support for using filgrastim as treatment of chemotherapy-induced febrile neutropenia 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 filgrastim in patients who have been receiving prophylactic filgrastim. Consider in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.

Support for using filgrastim in hematopoietic stem cell transplantation can be found in the National Comprehensive Cancer Network's guideline for hematopoietic stem cell transplantation. The NCCN Guideline supports the use of filgrastim as treatment for hematopoietic cell mobilization for autologous donors in combination with any of the following: plerixafor, in combination with cyclophosphamide with or without plerixafor, as a single agent, or in combination with disease-specific chemotherapy with or without plerixafor. Filgrastim can also be used as treatment for hematopoietic cell mobilization for allogenic donors as a single agent. Finally, filgrastim can be used as additional therapy for insufficient collection of stem cells in combination with plerixafor following treatment with filgrastim alone or filgrastim and disease-specific chemotherapy.

Support for using filgrastim in the management of CAR T-cell-related toxicities can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-related toxicities. Filgrastim can be considered as supportive care for neutropenic patients.

Support for using filgrastim in patients with acute myeloid leukemia can be found in the National Comprehensive Cancer Network's guideline for acute myeloid leukemia. The NCCN Guideline supports the use of filgrastim for treatment induction in patients who are candidates for intensive induction therapy with favorable-risk AML (CBF-AML, NPM1-mutated/FLT3 wild-type AML, in-frame bZIP mutation in CEBPA) in combination with fludarabine, high-dose cytarabine, and idarubicin plus gemtuzumab ozogamicin. Filgrastim can also be used for treatment induction in patients as part of an alternative non-anthracycline-containing regimen (eg, FLAG) who are candidates for intensive induction therapy who exceed anthracycline dose or have cardiac issues but are still able to receive aggressive therapy. It is appropriate to use filgrastim as a component of repeating the initial successful induction regimen if late relapse (≥12 months since induction regimen). Filgrastim can be used for relapsed/refractory disease in combination with cladribine and cytarabine, with or without mitoxantrone or idarubicin. Finally, filgrastim can be used for relapsed/refractory disease in combination with fludarabine and cytarabine, with or without idarubicin.

Support for using filgrastim in hairy cell leukemia can be found in the National Comprehensive Cancer Network's guideline for hairy cell leukemia. The NCCN Guideline indicates that neutrophil growth factors, such as filgrastim, are indicated for patients with neutropenic fever following systemic therapy.

Support for using filgrastim in chronic myeloid leukemia can be found in the National Comprehensive Cancer Network's guideline for chronic myeloid leukemia. The NCCN Guideline for chronic myeloid leukemia supports the use of granulocyte colony stimulating factors to overcome imatinib-induced neutropenia in patients with persistent neutropenia.

Support for using filgrastim to treat aplastic anemia is supported by two studies. In a series of 17 Japanese adults with severe aplastic anemia, an immunosuppressive regimen with concomitant granulocyte colony-stimulating factor (G-CSF) induced a good response in 82%. Dosing consisted of intravenous (IV) methylprednisolone 20 milligrams/kilogram/day (mg/kg/day) on days 1 to 3 with decreasing doses of 10 mg/kg/day to 2.5 mg/kg/day for days 4 to 6, anti-lymphocyte globulin or anti-thymocyte globulin 30 mg/kg/day for 5 days, oral cyclosporine 5 mg/kg/day initially then adjusted to maintain trough levels at 200 to 250 nanograms/milliliter, and subcutaneous G-CSF 250 micrograms/day. Good response was defined as meeting at least two of the following criteria: absolute reticulocyte, neutrophil, and platelet counts above 60,000/microliter, 1000/microliter and 50,000/microliter, respectively, or hemoglobin increase of greater than 2 grams/deciliter without transfusion. The median time to reach this endpoint in responders was 3 months. Three of 17 individuals died, including two non-responders and one responder who later developed paroxysmal nocturnal hemoglobinuria (PNH). Three other instances of PNH and one case of myelodysplastic syndrome ensued. Of 14 survivors (5.7 to 63.1 months of follow-up), only three did not require maintenance immunosuppression with or without G-CSF, or bone marrow transplant (Matsuo et al).
In a randomized trial of 69 children with moderate to severe acquired aplastic anemia, the addition of granulocyte colony-stimulating factor (G-CSF) to a multi-drug immunosuppressive regimen did not improve efficacy. 50 subjects classified as having very severe aplastic anemia (VSAA) (platelet, reticulocyte and neutrophil counts less than 20,000/microliter (mcL), 20,000/mcL and 200/mcL, respectively) were uniformly treated with a G-CSF-containing regimen. The overall trilineage response rates in the very severe aplastic anemia (VSAA), G-CSF +, and G-CSF - groups were not statistically significant at 3 months (47%, 39%, and 53%), 6 months (71%, 55%, and 77%), and 12 months (73%, 60%, and 73%), respectively. The 3 groups did not differ significantly with respect to survival, infectious complications, relapse rates, new cytogenetic abnormalities, or clonal disease evolution. Subjects received intravenous (IV) horse anti-thymocyte globulin (Lymphoglobuline(R)) 1.5 vials/10 kilograms (kg)/day infused over 12 hours for 5 days, methylprednisolone 2 milligrams (mg)/kg/day IV on days 1 to 7, then 1 mg/kg/day orally on days 8 to 14 and tapered to end on day 30, oral cyclosporine 6 mg/kg/day adjusted to maintain whole blood trough levels of 100 to 200 nanograms/milliliter on days 1 to 180, oral danazol 5 mg/kg/day on days 1 to 180, with (G-CSF +; n=35) or

without (G-CSF -; n=34) IV or subcutaneous G-CSF 400 micrograms/square meter days 1-90. G-CSF administration was changed to thrice weekly once the absolute neutrophil count reached 5x10(9) per liter. Drug treatment was well tolerated with drug-related toxicity similar among the G-CSF + and G-CSF - groups. The authors recommend against initial adjunctive G-CSF except in VSAA (Kojima et al).

Support for using filgrastim to treat neutropenia related to renal transplantation can be found in a case report by Derici et al. Neutropenia in a renal transplant patient was successfully treated with granulocyte colony-stimulating factor (G-CSF) (filgrastim; Neupogen(R)). One year after transplantation, a 32-year-old patient with end-stage renal disease was diagnosed with chronic rejection by biopsy and admitted to the hospital; chest X-ray revealed infiltration in the middle left lung. Fluconazole, azathioprine, and filgrastim 6 micrograms/kilogram/day subcutaneously were started. After G-CSF administration, fever resolved and the white cell count rose from 500/cubic millimeter to 22,7000/cubic millimeter; azathioprine was restarted. No rejection episodes or adverse effects were noted.

Support for using filgrastim for glycogen storage disease type I can be found in a guideline published by the American College of Medical Genetics and Genomics. Neutropenia and recurrent infections are a common manifestation of glycogen storage disease type 1. Administration of granulocyte colony stimulating factors like filgrastim increases blood neutrophil counts to normal or above normal levels. Neutropenic patients with GSD Ib should be treated with G-CSF, particularly if there is already a history and pattern of fever, infections, or enterocolitis. The lowest effective G-CSF dose should be used to avoid worsening of splenomegaly, hypersplenism, hepatomegaly, and bone pain. G-CSF should be administered subcutaneously starting at 0.5–1.0 µg per kilogram per day given daily or every other day. The G-CSF dose should be increased stepwise at approximately 2-week intervals until the target ANC of more than 500 to up to 1.0×109 /l is reached. This dose then should be maintained, adjusting for subsequent increases in the patient's weight with growth and development. Blood count with manual differential should be monitored several times per year. Bone marrow examinations are not recommended unless there is an unexpected change in the patient's other blood counts.

Support for using filgrastim to reduce neonatal sepsis in infants with preeclampsia-associated neutropenia can be found in a study by Kocherlakota et al. Filgrastim was found to be beneficial in increasing the absolute neutrophil count (ANC) and reducing the incidence of neonatal sepsis in infants with preeclampsia-associated neutropenia. In an unblinded study, patients (n=28) were assigned to conventional treatment or treatment with filgrastim (5 or 10 micrograms/kilogram (mcg/kg)/day). The ANC had doubled in 24 hours in the 10 mcg/kg group and no change was seen in the 5 mcg/kg group or conventional treatment group. In the filgrastim group, 13% were diagnosed with sepsis, whereas 54% in the conventional treatment group were.

Support for using filgrastim to reduce infectious complications following esophagectomy can be found in a small study by Schafer et al. When compared to patients in a historical control group (n=77), filgrastim administration to patients with esophageal cancer undergoing esophagectomy (n=20) resulted in a significant reduction in the infection rate during the 10 days following surgery. Patients in the study group were given filgrastim 300 micrograms/day (mcg/day) subcutaneously to 480 mcg/day depending on body weight starting 2 days before surgery and discontinued on day 7 following surgery. Ten days following surgery, no complications had occurred in the study group; however, 29.9% of patients (n=23) in the control developed infections (p=0.008). For postoperative days 11 and up, the significant difference in infection between the two groups was not maintained.

Support for using filgrastim to improve neutrophil count in Shwachman syndrome can be found in a case report by Adachi et al. Filgrastim has successfully treated a 1.5-year-old male with Shwachman syndrome. Improvement in the neutrophil count (from 552/microliter (mcL) to 45,300/mcL) occurred following 7 days of filgrastim therapy (100 micrograms/square meter).

Support for using filgrastim to treat neutropenia caused by HIV can be found in guidelines issued by the U.S. Public Health Service (USPHS). Administration of granulocyte-macrophage (GM-CSF) may be considered for patients with human immunodeficiency virus (HIV) infection to reverse neutropenia. This use, however, would

not be routinely indicated. The recommended dosage is 5 to 10 micrograms/square meter/day given subcutaneously for 2 to 4 weeks.

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Reference number(s)
4799-A

STANDARD MEDICARE PART B MANAGEMENT

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:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

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Reference number(s)
2063-A

STANDARD MEDICARE PART B MANAGEMENT

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.

VII. REFERENCES

1. Nucala [package insert]. Research Triangle Park, NC: GlaxoSmithKline; January 2022.

2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2021 update. Available at: https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Accessed March 11, 2023.
3. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198-1207.
4. National Institutes of Health. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma - Full Report 2007. Bethesda, MD: National Heart Lung and Blood Institute; August 2007. Available at: https://www.ncbi.nlm.nih.gov/books/NBK7232/pdf/Bookshelf_NBK7232.pdf. Accessed March 11, 2023.
5. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. 2017:18;376(20):1921-1932.
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.
7. 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.
8. WJ Fokkens, VJ Lund, C Hopkins, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology.* 2020;58(Suppl S29):1-464.
9. Hopkins C. Chronic Rhinosinusitis with Nasal Polyps. *N Engl J Med.* 2019;381(1):55-63.
10. Agache I, Akdis CA, Akdis M, et al: EAACI Biologicals Guidelines-recommendations for severe asthma. Allergy 2021; 76(1):14-44.
11. Chung SA, Langford CA, Maz M, et al: 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2021; 73(8):1366-1383.

Reference number(s)
4582-A

STANDARD MEDICARE PART B MANAGEMENT

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 cyclic pyranopterin monophosphate (cPMP) 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 gene 1 *(MOSC1)*.
B. Continuation requests (where applicable):
    1. Genetic testing results documenting a mutation in the molybdenum cofactor synthesis gene 1 *(MOSC1)*.
    2. Chart notes or medical records documenting a benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for encephalopathy, 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 gene 1 *(MOSC1).*

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 Nulibry
B. Nulibry 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 gene 1 *(MOSC1).*
    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, seizure activity, improved or normalized uric acid, urinary S-sulfocysteine, and xanthine levels).

V. REFERENCES

1. Nulibry [package insert]. Boston, MA: Origin Biosciences, Inc.; February 2021.
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/ct2/show/NCT02629393. Accessed: October 27, 2022.
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 27, 2022.

Reference number(s)
4850-A

STANDARD MEDICARE PART B MANAGEMENT

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 congenital hemophilia A or 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. REFERENCES

1. Obizur [package insert]. Lexington, MA: Baxalta US Inc.; September 2021.
2. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised March 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed December 3, 2022.
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.

Reference number
6242-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4238-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
5326-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Opdualag [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; March 2022.

Reference number(s)
2210-A

STANDARD MEDICARE PART B MANAGEMENT

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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3. Smolen JS, Landewé R, Bijlsma J, 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*:685-699.
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8. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 12, 2023.
9. 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.
10. 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.
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13. 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.
14. Westhovens R, Robles M, Ximenes AC, et al: Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009; 68(12):1870-1877.
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Reference number(s)
4397-A

STANDARD MEDICARE PART B MANAGEMENT

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: Molecular genetic tests showing a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene or liver enzyme analysis demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity.

III. CRITERIA FOR INITIAL APPROVAL

Primary hyperoxaluria type 1
Authorization of 12 months may be granted for treatment of primary hyperoxaluria type 1 (PH1) when the member has a documented diagnosis of primary hyperoxaluria type 1 (PH1) confirmed by either:
A. Molecular genetic test showing a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene.
B. Liver enzyme analysis demonstrating absent or significantly reduced alanine:glyoxulate 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. Benefit is defined as a decrease or normalization of urinary and/or plasma oxalate.

V. REFERENCES

1. Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; October 2022.
2. Niaudet, P. Primary hyperoxaluria. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022.
3. Milliner DS. The primary hyperoxalurias: an algorithm for diagnosis. Am J Nephrol 2005; 25:154.

Reference number(s)
6203-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
2390-A

STANDARD MEDICARE PART B MANAGEMENT

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. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
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 men and women with glucocorticoid-induced osteoporosis at high risk for 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. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
4. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures.
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 the treatment of osteoporosis in men or postmenopausal women at high risk for fracture.

B. Osteoporosis prevention
Authorization of 12 months may be granted for the 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. Treatment of men and women with glucocorticoid-induced osteoporosis at high risk for fracture
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. The member is receiving the requested medication for an indication listed 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 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 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.; May 2022.
2. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado. Available at https://www.micromedexsolutions.com Accessed October 18,2022.
3. The NCCN Drugs & Biologics Compendium™ © 2022 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed October 18, 2022.

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.

Reference number(s)
5915-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Qalsody [package insert]. Cambridge, MA: Biogen MA, Inc.; April 2023.

Reference number(s)
2066-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
4717-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
5693-A

STANDARD MEDICARE PART B MANAGEMENT

REBYOTA (fecal microbiota, live - jslm)

POLICY

I. 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
Rebyota is indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Limitations of Use
Rebyota is not indicated for the treatment of CDI.

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. Medical records, chart notes, and/or lab test results documenting the following:
   1. Recurrent CDI infection
   2. Stool test confirming the presence of toxigenic *C. difficile*

III. EXCLUSIONS

Coverage will not be provided for members requesting Rebyota for the treatment of CDI.

IV. CRITERIA FOR INITIAL APPROVAL

Prevention of recurrence of Clostridioides difficile infection (CDI)
Authorization of 30 days for a one-time treatment may be granted for prevention of CDI when all of the following criteria are met:
   A. Member is 18 years of age and older
   B. Member has recurrent CDI infection including either of the following:
      1. At least one recurrence after a primary episode and had completed at least 1 round of standard-of-care oral antibiotic therapy (e.g., metronidazole, vancomycin)
      2. Had at least 2 episodes of severe CDI resulting in hospitalization within the last year

C. Member has a positive stool test for the presence of toxigenic *C. difficile* within 30 days prior to treatment
D. A single, one-time 150 mL dose will be administered rectally 24 to 72 hours after the last dose of antibiotics

V. REFERENCES

1. Rebyota [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc; November 2022.

Reference number(s)
4475-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
2501-A

STANDARD MEDICARE PART B MANAGEMENT

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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Reference number(s)
4824-A

STANDARD MEDICARE PART B MANAGEMENT

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

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Reference number(s)
6041-A

STANDARD MEDICARE PART B MANAGEMENT

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.
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Reference number(s)
4878-A

STANDARD MEDICARE PART B MANAGEMENT

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

1. Saphnelo [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2023.
2. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2023 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. *Ann Rheum Dis*. 2024;83:15-29.
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Reference number(s)
4695-A

STANDARD MEDICARE PART B MANAGEMENT

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.

A. 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.

A. 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:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat Hemophilia A or B with inhibitors

3. 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. REFERENCES

1. Sevenfact [package insert]. Les Ulis, France: Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.); April 2020.
2. IBM Micromedex [Internet database]. Ann Arbor, MI: Truven Health Analytics. Updated periodically. Accessed December 3, 2022.
3. 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.
4. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised March 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed December 3, 2022.

Reference number(s)
2749-A

STANDARD MEDICARE PART B MANAGEMENT

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
   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 (2mg 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 (2mg 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 (2mg 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. 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 January 8, 2023.
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Reference number
2394-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number
1632-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.
7. Preis M, Lowrey CH. Laboratory tests for paroxysmal nocturnal hemoglobinuria (PNH). Am J Hematol. 2014;89(3):339-341.
8. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.

Reference number(s)
5582-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
2133-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
4213-A

STANDARD MEDICARE PART B MANAGEMENT

SPRAVATO (esketamine) nasal spray

POLICY

I. 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
Spravato is indicated, in conjunction with an oral antidepressant, for the treatment of:
A. Treatment-resistant depression (TRD) in adults
B. Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Limitations of Use:
The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of Spravato does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of Spravato.

Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.

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. Pretreatment depression severity score(s) from standardized rating scale(s) that reliably measure depressive symptoms (e.g., Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.)
   2. Medical records documenting inadequate response with antidepressants for the current depressive episode (if applicable)
B. For continuation of therapy:
   Current depression severity score(s) from standardized rating scale(s) that reliably measure depressive symptoms (if applicable)

III. CRITERIA FOR INITIAL APPROVAL

A. Treatment-resistant depression (TRD)/Major Depressive Disorder (MDD) with acute suicidal ideation or behavior

Authorization of 1 month may be granted for treatment of TRD or MDD with acute suicidal ideation or behavior when all of the following criteria are met:

1. Member has a confirmed diagnosis of severe major depressive disorder (single or recurrent episode), documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS]).
2. The requested medication will be prescribed by or in consultation with a psychiatrist.
3. The requested drug will be administered under the direct supervision of a healthcare provider.
4. The requested drug will be used in combination with an oral antidepressant (e.g., duloxetine, escitalopram, sertraline, venlafaxine).
5. Member meets either of the following criteria:
    i. Member has experienced an inadequate response during the current depressive episode with two antidepressants (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine).
    ii. Member has current suicidal ideation with intent defined as both of the following:
        a. Member has thoughts, even momentarily, of self-harm with at least some intent or awareness that they may die as a result, or member thinks about suicide.
        b. Member intends to act on thoughts of killing themselves.

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. Treatment-resistant depression (TRD)

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

1. The member is currently receiving therapy with Spravato
2. Spravato is being used to treat treatment-resistant depression
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. An improvement or sustained improvement from baseline in depressive symptoms documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS]).

B. Major depressive disorder (MDD) with acute suicidal ideation or behavior

1. If the member has not received 1 full month of therapy, then authorization for up to 1 month to complete a treatment course may be granted when all the following criteria are met:
    i. The member is currently receiving therapy with Spravato
    ii. Spravato is being used to treat major depressive disorder with acute suicidal ideation or behavior
    iii. The member is receiving benefit from therapy. Benefit is defined as:
        a. An improvement or sustained improvement from baseline in depressive symptoms documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS]).
2. If the member has completed one full month of therapy, then member must meet all initial criteria for approval. The use of Spravato beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in members with MDD with acute suicidal ideation or behavior.

V. REFERENCES

1. Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; July 2020.

Reference number(s)
4213-A

Reference number
2393-A

STANDARD MEDICARE PART B MANAGEMENT

STELARA (ustekinumab)
WEZLANA (ustekinumab-auub)

POLICY

I. 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. For the treatment of adult patients with moderately to severely active Crohn's disease (CD).
   2. For the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

   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. 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).

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 benefit of therapy.

B. Immune checkpoint inhibitor-related toxicity
   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

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. 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. 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 Stelara or Wezlana.
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 Stelara and its biosimilars.
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 and its biosimilars 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 or Wezlana 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 or Wezlana for mild (G1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin. Additionally, consider Stelara or Wezlana for infliximab- and/or vedolizumab-refractory moderate (G2) or severe (G3-4) diarrhea or colitis.

VII. REFERENCES

1. Stelara [package insert]. Horsham, PA: Janssen Biotech, Inc.; August 2022.
2. Wezlana [package insert]. Thousand Oaks, CA: Amgen Inc.; October 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.
5. Rubin DT, Ananthakrishnan AN, et al. 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol.* 2019;114:384-413.
6. 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.
7. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 15, 2024.
8. NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 1.2024. Available at: www.nccn.org. Accessed January 15, 2024.
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.
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12. Self-Administered Drug Exclusion List: (A53032). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
13. Self-Administered Drug Exclusion List: (A53033). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
14. Self-Administered Drug Exclusion List: Medical Policy Article (A53021). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
15. Self-Administered Drug Exclusion List: (SAD List) (A52800). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
16. Self-Administered Drug Exclusion List: (A53127). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
17. Self-Administered Drug Exclusion List: (A53066). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.

18. Self-Administered Drug Exclusion List: Medical Policy Article (A53022). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.

Reference number(s)
5046-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
5794-A

STANDARD MEDICARE PART B MANAGEMENT

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

Reference number(s)
2670-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
6123-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
5658-A

STANDARD MEDICARE PART B MANAGEMENT

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.

A. 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.

B. Compendial Use
Progressive 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 relapsed, refractory or progressive 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. REFERENCES

1. Tecvayli [package insert]. Horsham, PA: Janssen Biotech, Inc.; October 2022.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed November 2, 2022.

Reference number(s)
4731-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4701-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
6423-A

STANDARD MEDICARE PART B MANAGEMENT

TEVIMBRA (tislelizumab-jsgr)

POLICY

I. 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
Tevimbra as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 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. CRITERIA FOR INITIAL APPROVAL

Esophageal squamous cell carcinoma
Authorization of 12 months may be granted for the treatment of unresectable or metastatic esophageal squamous cell carcinoma when the following criteria are met:
A. The member has tried prior systemic chemotherapy not including a PD-L1 inhibitor
B. 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 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 Tevimbra.
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: Esophageal and esophagogastric junction cancer

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

V. EXPLANATION OF RATIONALE

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

VI. REFERENCES

1. Tevimbra [package insert]. San Mateo, CA: BeiGene USA, Inc; March 2024.

Reference number(s)
5106-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
4371-A

STANDARD MEDICARE PART B MANAGEMENT

THROMBATE III (Antithrombin III [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. Indicated in patients with hereditary antithrombin deficiency for treatment and prevention of thromboembolism
2. Indicated in patients with hereditary antithrombin deficiency for prevention of peri-operative and peri-partum thromboembolism

B. Compendial Uses
1. Acquired antithrombin III deficiency
2. Heparin resistance prior to and during cardiopulmonary bypass (CPB)
3. Sickle cell-thalassemia, treatment of chronic leg ulcers

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. Hereditary Antithrombin Deficiency
1. Authorization of 12 months may be granted for treatment of hereditary antithrombin deficiency when the requested medication will be used for any of the following indications:
   i. Treatment of thromboembolism
   ii. Prevention of thromboembolism
2. Authorization of 1 month may be granted for the treatment of hereditary antithrombin deficiency when the requested medication will be used for any of the following indications:
   i. Prevention of peri-operative (i.e., surgical procedures) thromboembolism
   ii. Prevention of peri-partum (i.e., obstetrical procedures) thromboembolism

B. Acquired Antithrombin Deficiency
Authorization of 6 months may be granted for treatment of acquired antithrombin deficiency when both of the following criteria is met:

1. The member has a condition associated with low levels of antithrombin III (e.g., disseminated intravascular coagulation (DIC) associated with sepsis or trauma, liver failure, asparaginase-induced antithrombin deficiency)
2. The requested medication will be used for the treatment or prophylaxis of thromboembolism

C. Heparin Resistance
Authorization of 1 month may be granted for treatment of heparin resistance prior to and during cardiopulmonary bypass (CPB).

D. Sickle cell beta thalassemia
Authorization of 3 months may be granted for treatment of chronic leg ulcers in patients with sickle cell beta thalassemia

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 Thrombate III
B. Thrombate III is being used to treat hereditary antithrombin deficiency (excluding prevention of peri-operative and peri-partum thromboembolism), acquired antithrombin deficiency, or sickle cell beta thalassemia
C. The member is receiving benefit from therapy.

IV. REFERENCES

1. Thrombate III [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC; October 2021.
2. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com (cited: October 17, 2022).
3. Hunault-Berger M, Chevallier P, Delain M, et al. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. Haematologica. 2008;93(10):1488-1494.

Reference number(s)
4821-A

STANDARD MEDICARE PART B MANAGEMENT

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.

VII. REFERENCES

1. Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corp.; October 2023.
2. Treprostinil [package insert]. Princeton, NJ: Sandoz, Inc.; April 2023
3. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J.* 2019; 53: 1802148; DOI: 10.1183/13993003.02148-2018. Published 24 January 2019.
4. 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.
5. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: 04/04/2023).
6. 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.
7. Berman S, Quick R, Yoder P, et al.. Treprostinil sodium (Remodulin), a prostacyclin analog, in the treatment of critical limb ischemia: open-label study. *Vascular* 2006; 14(3):142-148.
8. Mohler ER, Klugherz B, Goldman R, et al. Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication. *Vasc Med* 2000; 5:231-237.
9. 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.
10. External Infusion Pumps- Policy Article (A52507) Version R31. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed October 2, 2023.

Reference number(s)
5002-A

STANDARD MEDICARE PART B MANAGEMENT

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 Tretten.
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. REFERENCES

1. Tretten [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; June 2020.
2. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised March 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed October 4, 2022.

CVS caremark®

Reference number(s)
2195-A

STANDARD MEDICARE PART B MANAGEMENT

TYMLOS (abaloparatide)

POLICY

I. 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 postmenopausal women with osteoporosis at high risk for fracture (defined as history of osteoporotic fracture or multiple risk factors for fracture) or patients who have failed or are intolerant to other available osteoporosis therapy.
B. Treatment to increase bone density 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.

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

Osteoporosis treatment
Authorization of 12 months may be granted for the treatment of osteoporosis in men or postmenopausal women.

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 Tymlos
B. Tymlos is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy.

IV. OTHER

The cumulative duration of parathyroid hormone analogs (teriparatide and abaloparatide) will not exceed a total of 24 months in the member's lifetime.

V. REFERENCES

1. Tymlos [package insert]. Waltham, MA: Radius Health, Inc. December 2022.
2. Miller PD, Hattersley G, Riis BJ, et al. Effect of Abalaoparatide Vs Placebo on New Vertebral Fractures in Postmenopausal Women with Osteoporosis: A Randomized Clinical Trial. *JAMA*. 2016; 316 (7): 722:733.
3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis 2020. Endocr Pract. 2020;26 (Suppl 1):1-46.

Reference number(s)
4822-A

STANDARD MEDICARE PART B MANAGEMENT

Tyvaso (treprostinil inhalation 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.

FDA-Approved Indications

A. Treatment of Pulmonary arterial hypertension (PAH; World Health Organization [WHO] Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with New York Heart Association (NYHA) Functional Class III symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
B. Treatment of Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and WHO Group 3 connective tissue 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

Pulmonary Hypertension (PH)
Authorization of 12 months may be granted for treatment of pulmonary hypertension when both of the following criteria are met:

A. Member has either of the following:
    1. WHO Group 1 class of pulmonary hypertension (refer to Appendix)
    2. Pulmonary hypertension associated with interstitial lung disease (WHO Group 3)
B. Pulmonary hypertension was confirmed by either criterion (1) or criterion (2) below:
    1. Pretreatment right heart catheterization with all of the following results:
        a. Mean arterial pressure (mPAP) > 20 mmHg
        b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg
        c. Pulmonary vascular resistance (PVR) ≥ 3 Wood units in adult patients or pulmonary vascular resistance index (PVRI) ≥ 3 Wood units x m^2 in pediatric patients
    2. For infants less than one year of age, pulmonary hypertension was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed.

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.

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. Benefit is defined as either:
    1. Disease stability
    2. 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. REFERENCES

1. Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corp.; May 2022.
2. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J.* 2019; 53: 1802148; DOI: 10.1183/13993003.02148-2018. Published 24 January 2019.
3. 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.
4. 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

Reference number(s)
5682-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
2836-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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)

Reference number(s)
4722-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
4823-A

STANDARD MEDICARE PART B MANAGEMENT

Ventavis (iloprost inhalation 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.

FDA-Approved Indication
Ventavis is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (New York Heart Association [NYHA] Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

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

Pulmonary Arterial Hypertension (PAH)
Authorization of 12 months may be granted for treatment of PAH when ALL of the following criteria are met:
A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).
B. PAH was confirmed by either criterion (1) or criterion (2) below:
    1. Pretreatment right heart catheterization with all of the following results:
        a. Mean pulmonary arterial pressure (mPAP) > 20 mmHg
        b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg
        c. Pulmonary vascular resistance (PVR) ≥ 3 Wood units in adult patients or pulmonary vascular resistance index (PVRI) ≥ 3 Wood units x m^2 in pediatric patients
    2. For infants less than one year of age, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed.

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.

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. Benefit is defined as either:
    1. Disease stability
    2. 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. REFERENCES

1. Ventavis [package insert]. Titusville, NJ: Actelion Pharmaceuticals US, Inc.; March 2022.
2. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J.* 2019; 53: 1802148; DOI: 10.1183/13993003.02148-2018. Published 24 January 2019.
3. 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.
4. 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.

Reference number(s)
6135-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4835-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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
3. Clinical Consult: CVS Caremark Clinical Programs Review. Focus on Neuromuscular Disorders Clinical Programs. September 2020.

Reference number(s)
1984-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4868-A

STANDARD MEDICARE PART B MANAGEMENT

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 Vonvendi.
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. REFERENCES

1. Vonvendi [package insert]. Lexington, MA: Baxalta US Inc.; January 2022.
2. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised March 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed October 4, 2022.
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.

Reference number(s)
4388-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Vyepti [package insert]. Bothell, WA: Lundbeck Seattle BioPharmaceuticals, Inc.; April 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

Reference number(s)
4818-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
5108-A

STANDARD MEDICARE PART B MANAGEMENT

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. 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.

Reference number(s)
4870-A

STANDARD MEDICARE PART B MANAGEMENT

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. REFERENCES

1. Wilate [package insert]. Hoboken, NJ: Octapharma USA Inc.; November 2019.
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 other bleeding disorders. Revised March 2022. MASAC Document #272.

https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed October 4, 2022.
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 4, 2022.
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.

Reference number(s)
5561-A

STANDARD MEDICARE PART B MANAGEMENT

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-CNS 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. REFERENCES

1. Xenpozyme [package insert]. Cambridge, MA: Genzyme Corporation; August 2022.

Reference number(s)
2392-A

STANDARD MEDICARE PART B MANAGEMENT

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 Use
1. Treatment for osteopenia or osteoporosis in patients with systemic mastocytosis
2. Thyroid cancer as palliative care for bone metastases
3. Prevention of skeletal-related events in prostate cancer in patients with 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 any of the following:
1. For the prevention of skeletal-related events in members with bone metastases from a solid tumor (i.e., 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 the bone
Authorization of 12 months may be granted for the treatment of giant cell tumor of bone

D. Hypercalcemia of malignancy
Authorization of 2 months may be granted for the treatment of hypercalcemia of malignancy

E. Systemic mastocytosis
Authorization of 12 months may be granted for the treatment of osteopenia or osteoporosis in patients 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 2 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:
    a. Disease stability, or
    b. 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:
    a. Disease stability, or
    b. 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
C. Prevention of skeletal-related events associated with bone metastases from prostate 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.

Support for using Xgeva for the prevention of skeletal-related events in patients with bone metastases associated with prostate cancer can be found in the National Comprehensive Cancer Network's guideline for prostate cancer. The NCCN Guideline for prostate cancer supports the use of Xgeva as the preferred agent to prevent skeletal-related events in patients with castration-resistant prostate cancer who have documented bone metastases and creatinine clearance greater than 30 mL/min.

VI. REFERENCE

1. Xgeva [package insert]. Thousand Oaks, CA: Amgen Inc.; June 2020.
2. The NCCN Drugs & Biologics Compendium™ © 2021 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed October 18, 2022.

Reference number(s)
5047-A

STANDARD MEDICARE PART B MANAGEMENT

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

1. Xipere [package insert]. Bridgewater, NJ: Bausch & Lomb Americas, Inc.; February 2022
2. Yeh S, Khurana RN, Shah M, et al. Efficacy and Safety of Suprachoroidal CLS-TA for Macular Edema Secondary to Noninfectious Uveitis: Phase 3 Randomized Trial. Ophthalmology. 2020;127(7):948-955.

Reference number(s)
2546-A

STANDARD MEDICARE PART B MANAGEMENT

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.

VIII. REFERENCES

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Reference number(s)
4726-A

STANDARD MEDICARE PART B MANAGEMENT

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.

Reference number(s)
4816-A

STANDARD MEDICARE PART B MANAGEMENT

ZILRETTA (triamcinolone acetonide extended-release 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 Indication
Zilretta is indicated as an intraarticular injection for the management of osteoarthritis pain of the knee.

Limitation of Use: The efficacy and safety of repeat administration of Zilretta have not been demonstrated.

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

Osteoarthritis pain of the knee
Authorization of one dose per knee may be granted for treatment of osteoarthritis pain of the knee.

III. REFERENCES

1. Zilretta [package insert]. Burlington, MA: Flexion Therapeutics, Inc.; March 2022.

Reference number(s)
5851-A

STANDARD MEDICARE PART B MANAGEMENT

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 or recurrent locally advanced 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. REFERENCES

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