Medicare Advantage Medical Drug Policy

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Medicare Part B References & Summary of Evidence

Description

This document contains information regarding WyoBlue Advantage's Medicare Part B (medical) drugs requiring prior authorization and/or step therapy. For medical procedures, refer to the Medicare Coverage Database and WyoBlue Advantage's medical policies for applicable coverage policies.

Related Medical Coverage Policies

- This policy document is meant to be used alongside the following website:
    - Medicare Coverage Database Search (website to search for National and Local Coverage Determinations and Coverage Articles [NCD, NCA, LCD, and LCAs]: https://www.cms.gov/medicare-coverage-database/new-search/search.aspx

*Note: The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.

**Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Abecma® (idecabtagene vicleucel)
HCPCS: Q2055

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

- Abecma is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

- Safety and efficacy for use as third-line therapy in relapsed or refractory multiple myeloma was established in the KarMMa-3 trial, an open-label, phase 3 study of 386 patients with relapsed/refractory multiple myeloma who had received at least two prior lines of therapy that included an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody. The study excluded patients with an ECOG score of 2 or greater, a creatinine clearance of less than or equal to 45 mL/minute, alanine aminotransferase greater than 2.5 times upper limit of normal, and left ventricular ejection fraction less than 45%. Patients were also excluded if absolute neutrophil count less than 1000 cells/mm^3 and platelet count less than 75,000/mm^3. Patients were required to have measurable disease. The primary endpoint was progression free survival (PFS). The median PFS was 13.3 months in the Abecma group compared with 4.4 months in the standard-regimen group (hazard ratio for disease progression or death, 0.49; 95% confidence interval: 0.38, 0.65; p-value < 0.001). A response occurred in 71% of the patients in the Abecma group and in 42% of those in the standard-regimen group (p-value < 0.001); a complete response occurred in 39% and 5%, respectively.

- Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

- While use of Abecma has not been established in patients with a creatinine clearance of less than 45 mL/minute, other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other CAR-T therapies support their use in these patients,

Abecma should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 mL/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.

- While use of Abecma has not been established in patients with an alanine aminotransferase of greater than 2.5 times the upper limit of normal (ULN), other CAR-T therapies have been studied in subjects with an alanine aminotransferase of up to 5 times the ULN and the CTCAE recommendations have set 5 times the ULN as the cutoff for grade 2 adverse reactions. As the classification system uses 5 times the ULN and other CAR-T therapies have data supporting use in this patient population, Abecma should be tolerated in these patients as well. As there is no data to support administration of CAR-T at levels higher than 5 times the ULN, therapy should not be given to patients not meeting that threshold.

- The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. While Abecma has only been studied in patients with a LVEF greater than or equal to 45%, there is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Abecma should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.

- A provider portal is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

1. Abecma [prescribing information]. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; July 2024.
2. National Comprehensive Cancer Network. Multiple myeloma (Version 1.2025). 2024 Sept 17. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed on March 21, 2025.
3. Munshi NC, Anderson Jr LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. NEJM. 2021 Feb 25; 384 (8): 705 - 16.
4. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (Version 5.0). 2017 Nov 27. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed on July 6, 2022.
5. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. NEJM. 2023 March 16; 388: 1002 – 14.

Policy History		
#	Date	Change Description
1.3	Effective Date: 06/06/2024	Updated to include the new indication for use as third line therapy
1.2	Effective Date: 10/12/2023	Updated to include preliminary criteria to allow use as third line therapy

1.1	Effective Date: 08/04/2022	Updated to align criteria across all CAR-T policies
1.0	Effective Date: 03/07/2022	New policy

Adakveo® (crizanlizumab-tmca)
HCPCS: J0791

Background Information:

- Sickle cell disease (SCD) is a recessive hemolytic anemia caused by a mutation in the β-globin gene. It is characterized by the formation of sickle hemoglobin (HbS). HbS is less soluble and less elastic than fetal hemoglobin (HbF) or normal adult hemoglobin (HbA). The disease involves multicellular adhesion between sickled red blood cells, white blood cells, platelets, and endothelial cells resulting in vaso-occlusive crises (VOCs). VOCs are the hallmark of SCD and are experienced by approximately 70% of patients. They are recurring, unpredictable, painful events that decrease organ function with complications including stroke, pneumonia, vision loss, pulmonary hypertension, leg ulcers, and sepsis. VOCs are often treated as an emergency requiring acute care and are the number one reason patients with SCD visit the emergency room or are hospitalized.

- Hydroxyurea is a ribonucleotide reductase inhibitor which increases the amount of circulating HbF in the body and has been a mainstay of therapy. It also has been shown to lower the number of circulating leukocytes and reticulocytes altering the expression of adhesion molecules; raise red blood cell (RBC) volume; and improve cellular deformability and rheology, all of which contribute to a decrease in VOCs. The 2014 National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease Guidelines recommend the use of hydroxyurea for the following patient populations:

    - In adults with SCD who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period
    - In adults with SCD who have sickle cell-associated pain that interferes with daily activities and quality of life
    - In adults with SCD who have a history of severe and/or recurrent acute coronary syndrome
    - In adults with SCD who have severe symptomatic chronic anemia that interferes with daily activities or quality of life
    - In infants 9 months of age and older, children, and adolescents with SCD, offer treatment with hydroxyurea regardless of clinical severity to reduce complications
    - In adults and children with SCD who have chronic kidney disease and are taking erythropoietin

- The guidelines recommend starting hydroxyurea at a dose of 15 mg/kg/day for adults and increasing the dose by 5 mg/kg/day every 8 weeks to a maximum dose of 35 mg/kg/day. A clinical response to therapy may take 3 – 6 months. Therefore, a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.

- Adakveo is a monoclonal antibody that is indicated to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older with sickle cell disease. It binds to P-selectin and blocks interactions between endothelial cells, platelets, RBCs, and leukocytes. P-selectin plays a role in the formation of the multicellular aggregates that lead to VOCs.

- The efficacy of Adakveo was evaluated in the SUSTAIN trial, a randomized, multicenter, placebo-controlled, double-blind trial of 198 patients with sickle cell disease of any genotype and a history of 2 - 10 VOCs in the previous 12 months. Patients were excluded if they were receiving long-

term red blood cell transfusions. The primary endpoint was the annual rate of VOCs leading to a healthcare visit. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered VOCs. Patients receiving Adakveo 5 mg/kg, had a lower median annual rate of VOC compared to those receiving placebo (1.63 vs. 2.98, p-value = 0.01) indicating a 45.3% lower rate with Adakveo. Thirty-six percent of patients treated with Adakveo did not experience a VOC compared to 17% in the placebo arm. The median time to first VOC from randomization was 4.1 months vs. 1.4 months in the Adakveo and placebo arm, respectively.

References:

1. Adakveo [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2024.
2. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. New Engl J Med. 2017; 376 (5): 429 – 439.
3. Ogedegbe HO. Sickle cell disease: an overview. Laboratory Medicine. 2002; 33(7): 515 – 543.
4. Yale SH, Nagib N, & Guthrie T. Approach to the vaso-occlusion crisis in adults with sickle cell disease. Am Fam Physician. 2000; 61(5): 1349 – 1356.
5. Kanter J & Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. Blood Rev. 2013; 27(6): 279 – 287.
6. Brousseau DC, Panepinto JA, Nimmer M, et al. The number of people with sickle-cell disease in the United States: national and state estimates. Am J Hematol. 2010; 85(1): 77 – 78.
7. National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: expert panel report, 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/publications/56-364NFULL.pdf. Accessed on: October 4, 2020.

Policy History		
#	Date	Change Description
1.3	Effective Date: 12/04/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 12/12/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 12/14/2023	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Adstiladrin® (nadofaragene firadenovec-vncg)
HCPCS: J9029

Background Information:

- Bladder cancer is one of the more common forms of cancer. Approximately 75% - 80% of newly diagnosed bladder cancers are classified as NMIBC – a type of cancer that has grown through the lining of the bladder but hasn't yet invaded the muscle layer. This type of cancer is associated with high rates of recurrence (between 30 to 80%) and the risk of progression to invasive and metastatic disease.

- Treatment and care of patients with high-risk NMIBC, including those with CIS, often involves removing the tumor followed by BCG bladder instillation therapy to reduce the risk of recurrence. Few effective treatment options exist for patients who develop BCG-unresponsive disease. The failure to achieve a complete response, or the disappearance of all signs of cancer as seen on cystoscopy, biopsied tissue, and urine, is associated with an increased risk of death or a disease-worsening event.

- Adstiladrin is a non-replicating adenoviral vector-based gene therapy indicated for the treatment of adult patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumors. It offers an additional treatment option in a historically limited space.

- The 2025 National Comprehensive Cancer Network Bladder Cancer Treatment Guidelines recommend TURBT for staging followed by a single dose of intravesicular mitomycin or gemcitabine as the first step in treatment. Following the tumor evaluation, if the tumor is considered high-grade, BCG is the preferred adjuvant therapy and intravesicular mitomycin or gemcitabine provide additional options to those who aren't candidates for BCG therapy. BCG is typically given weekly for 6 weeks at induction followed by maintenance of 3 weekly instillations at month 3, 6, 12, 18, 24, 30, and 36. Two 6-week BCG induction courses should be completed before the patient is considered non-responsive to the therapy. If patients have had recurrence or are considered non-responsive to BCG therapy, cystectomy, Keytruda®, Anktiva®, or Adstiladrin are currently recommended as second-line therapies.

- Safety and efficacy were evaluated in CS-003, an open-label, multicenter, single-arm trial in 157 adults with BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors following transurethral resection, of whom 98 were considered evaluable for response. BCG-unresponsive high-risk NMIBC was defined as persistent disease following adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG was defined as the administration of at least five of six doses of an initial induction course plus either at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Patients were excluded from the trial if they had an ECOG score greater than 2 or had concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra. All visible papillary tumors were resected and those with persistent T1 disease on TURBT should undergo an additional re-TURBT within 14 to 60 days prior to beginning therapy. Patients received Adstiladrin once every three months for up to 12 months, until unacceptable toxicity, or recurrent high-grade NMIBC. Overall, 51% of enrolled patients using Adstiladrin therapy achieved a complete response and median duration of response was 9.7 months. Forty-six percent of responding patients remained in complete response for at least one year.

References:

1. Adstiladrin [prescribing information]. Kastrup, Denmark: Ferring Pharmaceuticals; October 2025.
2. Boorjian SA, Alemozaffar M, Konet BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. Lancet Oncol. 2021 Jan; 22 (1): 107 - 17.
3. National Comprehensive Cancer Network. Bladder cancer (Version 2.2025). 2025 Oct 10. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed on December 1, 2025.

Policy History		
#	Date	Change Description
1.4	Effective Date: 02/12/2026	Updated to clarify BCG unresponsive disease requirements
1.3	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/03/2024	Updated to remove requirements that all visible papillary tumors must be resected and those with persistent T1 disease on transurethral resection of bladder tumor (TURBT) should undergo an additional re-TURBT within 14 to 60 days prior to beginning Adstiladrin and patient must not have concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra
1.0	Effective Date: 07/01/2023	New Policy

Adzynma (ADAMTS13, recombinant-krhn)
HCPCS: J7171

Background Information:

- Congenital thrombotic thrombocytopenic purpura (cTTP) is an autosomal recessive disorder caused by biallelic mutations on the ADAMTS13 gene. It is characterized by less than 10% ADAMTS13 enzyme activity and the accumulation of ultra-large von Willebrand factor (VWF). The buildup of ultra-large VWF multimers leads to uncontrolled platelet aggregation, platelet adhesion, and abnormal clotting in the small blood vessels. cTTP often causes seemingly mild and nonspecific symptoms such as lethargy, headache, loss of concentration, and abdominal discomfort. In many patients, symptoms are ongoing without a clear time of onset or resolution. Thrombocytopenia and microangiopathic hemolytic anemia can occur, but neurologic symptoms can occur without thrombocytopenia or anemia, and thrombocytopenia may occur without apparent hemolysis. Acute, severe exacerbations are uncommon but may be life-threatening without appropriate treatment. Exacerbations of the disease can be triggered during the neonatal period, pregnancy, infections, or surgeries although none of these has to occur for an acute attack to happen.

- The 2020 International Society on Thrombosis and Haemostasis (ISTH) good practice statements for the clinical care of patients with thrombotic thrombocytopenic purpura (TPP) state TTP should be considered in individuals presenting with thrombocytopenia and microangiopathic hemolytic anemia. cTTP should be suspected in individuals with any of the following presentations: severe neonatal hyperbilirubinemia, recurrent thrombocytopenia in a child or young adult, transient neurologic symptoms of stroke in a child or young adult, embolic stroke of undetermined source, or new onset TTP and absence of an ADAMTS13 inhibitor. Once suspected, patients should be tested for decreased ADAMTS13 enzyme activity, and if the enzymatic activity is less than 10% of normal without ADAMTS13 antibodies, genetic testing showing biallelic mutations in the ADAMTS13 gene will be confirmatory of cTPP.

- The standard of care for cTTP up until now has been plasma transfusions. Plasma transfusions allow for rapid replacement of ADAMTS13 during an acute attack and can be used prophylactically to minimize the risk of future attacks. The main complications of plasma infusion are allergic reactions. These may be treated or prevented using antihistamines. If allergic reactions are severe, other therapies, such as, a plasma-derived factor VIII concentrate that contains ADAMTS13 may be used.

- Adzynma provides an additional treatment option for cTTP. It is a human recombinant ADAMTS13 indicated for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with cTTP.

- Safety and efficacy of Adzynma were evaluated in a Phase III, randomized, controlled, open-label, crossover, trial of 46 patients with cTTP. Patients were randomized to receive 6 months of treatment with either 40 IU/kg Adzynma or plasma-based therapies during the first period of the trial and then crossed over to receive the other treatment for 6 months during the second period. The mean annualized event rate of thrombocytopenia manifestations was 2.0 for patients receiving Adzynma (9 of 37 patients) compared to 4.44 in patients receiving plasma-based therapies (19 of 38 patients). Pharmacokinetic results showed patients (n = 23) receiving 40 IU/kg Adzynma IV achieved a four- to five-fold increase in ADAMTS13 enzyme activity after a single infusion compared to plasma-based therapies.

- Adzynma has not been studied and there is no data to support use in combination with other medications or treatment modalities used to treat cTTP.

References:

1. Adzynma [prescribing information]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; June 2024.
2. Kremer Hovinga JA & George JN. Hereditary thrombotic thrombocytopenic purpura. NEJM. 2019 Oct 24; 381 (17): 1653 – 62.
3. Alwan F, Vendramin C, Liesner R, et al. Characterization and treatment of congenital thrombotic thrombocytopenic purpura. Blood. 2019 Apr 11; 133 (15): 1644 - 51.
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7. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct; 18: 2496 – 502.
8. Clinicaltrials.gov. A study of BAX 930 in children, teenagers, and adults born with thrombotic thrombocytopenic purpura (TTP) (NCT03393975). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT03393975. Accessed on November 13, 2023.
9. Clinicaltrials.gov. A study of TAK-755 in participants with congenital thrombotic thrombocytopenic purpura (NCT04683003). Available at: https://classic.clinicaltrials.gov/ct2/show/study/NCT04683003. Accessed on November 13, 2023.

Policy History		
#	Date	Change Description
1.2	Effective Date: 12/04/2025	Annual review of criteria was performed, no changes were made

1.1	Effective Date: 12/12/2024	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 03/01/2024	New policy

Aflibercept Products
Aflibercept-yszy Q5153
AhzantiveTM (aflibercept-mrbb) Q5150
EnzeevuTM (aflibercept-abzv) Q5149
Eydenzelt® (aflibercept-boav) J3590
Eylea® (aflibercept) J0178
Eylea® HD (aflibercept) J0177
OpuvizTM (aflibercept-yszy) Q5153
PavbluTM (aflibercept-ayyh) Q5147
YesafiliTM (aflibercept-jbvf) Q5155

Background Information:

- Intravitreal injections of anti-vascular endothelial growth factor (VEGF) have been widely used by ophthalmologists to treat a variety of ocular diseases. They are injected directly into the eye to prevent the formation of new blood vessels and reduce blood vessel leakage and inflammation. Eylea is currently approved to treat the following indications: diabetic macular edema (DME), diabetic retinopathy (DR), macular edema due to retinal vein occlusion (RVO), neovascular (wet) age related macular degeneration (AMD), and ROP. Eylea HD is currently approved for use in wet AMD, DME, and DR. Ahzantive, Opuviz, Pavblu, and Yesafili are approved for use in wet AMD, RVO, DME, and DR. Enzeevu is approved for use in wet AMD.

- Age-related Macular Degeneration

    - Age-related macular degeneration is a degenerative disease of the macula that results primarily in loss of central vision. Wet AMD is characterized by growth of abnormal vessels into the subretinal space. These abnormal blood vessels leak leading to collections of subretinal fluid and/or blood beneath the retina. The 2022 American Academy of Ophthalmologists (AAO) Age-Related Macular Degeneration Preferred Practice Pattern Guidelines recommend observation and early detection, antioxidant vitamin and mineral supplements, and intravitreal injections of anti-VEGF agents for the management of wet AMD. Guidelines recommend Eylea, Avastin®, Vabysmo™, or Lucentis® for treatment. The guidelines have not been updated with Beovu®, Byooviz™, and Susvimo™.

- Diabetic retinopathy and Diabetic Macular Edema

    - DR and DME are common complications and the ocular manifestations of end-organ damage in diabetes mellitus. The 2022 AAO Diabetic Retinopathy Preferred Practice Pattern Guidelines state the goals of therapy for DR and DME include improvement or stabilization of visual function, improvement in vision-related quality of life, and optimal control of blood glucose, blood pressure, and other metabolic risk factors. Patients should always be treated with anti-VEGF therapy if they have severe non-proliferative DR or proliferative DR with center-involved macular edema. In cases of mild to moderate non-proliferative DR with center-involved macular edema, patients should also receive intravitreal injections. The guidelines support the use of Lucentis, Eylea, Vabysmo, and Avastin. AAO recommendations were based on trials comparing Eylea, Avastin, and Lucentis to focal laser treatment. All trials showed that

treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years compared to laser treatment.

- Retinal Vein Occlusion

    - Retinal vein occlusion occurs when there is partial or complete obstruction of a retinal vein. Vision loss can occur with RVO and is associated with macular ischemia or edema, retinal hemorrhages, vitreous hemorrhage, or epiretinal membrane formation. The 2019 AAO Retinal Vein Occlusions Preferred Practice Pattern Guidelines recommend anti-VEGF therapy as first-line treatment for macular edema caused by RVO. The guidelines support the use of Lucentis, Eylea, and Avastin. The guidelines state VEGF inhibitors, Eylea, Avastin, and Lucentis, are more effective than sham injection or laser therapy in maintaining or improving visual acuity in patients with macular edema secondary to RVO.

- There are very few randomized control trials that assess the efficacy of one anti-VEGF therapy over another. Of the two that are available, Avastin, Eylea, and Lucentis were all shown to be non-inferior to each other, and because of this, choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability. However, a 2015 study conducted by Wells, et al. did show Eylea was superior to Avastin therapy when patients had a visual acuity of less than or equal to 20/50. In addition, a sub-cohort analysis of the YOSEMITE and RHINE trials showed Vabysmo demonstrated BCVA gains similar to aflibercept, while demonstrating numerically greater improvements in anatomic outcomes at years 1 and 2. Therefore, in these scenarios Avastin should not be used prior to Eylea or Vabysmo.

- Retinopathy of Prematurity

    - ROP is a developmental vascular proliferative disorder that occurs in the retina of preterm infants with incomplete retinal vascularization and is an important cause of severe visual impairment in childhood. There have been over 50 different risk factors identified for development of ROP. The most common are low birth weight and low gestational age. ROP typically begins approximately 34 weeks post-menstrual age (PMA), although it may be seen as early as 30 to 32 weeks. It advances irregularly until 40 to 45 weeks PMA but resolves spontaneously in the majority of infants. Ocular outcome is typically poor in infants with severe untreated ROP. Among untreated eyes, poor structural outcomes occurred in 3.1% of eyes, and poor Snellen visual acuity occurred in 5.1% of eyes.

    - Pathogenesis is thought to occur in two steps. First, an initial injury caused by factors such as hypotension, hypoxia, or hyperoxia, with free radical formation, injures newly developing blood vessels and disrupts normal angiogenesis. Following this disruption, vessels either resume normal growth or new vessels grow abnormally out from the retina into the vitreous. Increased permeability of these abnormal new vessels can result in retinal edema and hemorrhage. Abnormal fibrovascular tissue may develop along with the neovascularization and later contract, producing traction on the retina. In some severe cases, this results in retinal distortion or retinal detachment. However, in most instances, the abnormal vascular tissue regresses with little residual effect.

    - The International Classification for Retinopathy of Prematurity (ICROP) provides a uniform approach to documenting the extent and severity of disease. Four features are evaluated:

    - Zone: describes the disease location on the retinal surface in relation to the disc, from the central zone (I) to the outer crescent (zone III)

    - Stage: describes the severity from mildest disease (flat white line of demarcation (stage 1)) to most severe (total retinal detachment (stage 5))
    - Extent: described by dividing the retinal surface in 12 sections, similar to hours of a clock

    - Presence or absence of plus disease, the most important indicator of disease severity. Pre-plus disease is an intermediate state between normal posterior pole vessels and plus disease. Plus disease is characterized by abnormal dilation and tortuosity of the posterior pole vessels.

- Treatment is initiated when the infant develops high-risk pre-threshold ROP, also called type I ROP. Type I ROP is defined as any of the following:

    - Any stage ROP with plus disease in zone I

    - Stage 3 ROP without plus disease in zone I

    - Stage 2 or 3 ROP with plus disease in zone II

- Treatment may consist of retinal ablative therapy with laser photocoagulation or intravitreal injection of an anti-VEGF agent. Eylea is the only FDA approved anti-VEGF for ROP although Avastin and Lucentis have also been used off-label for this patient population. The choice between the two treatment modalities is largely based on the experience and preference of the treating ophthalmologist and the preferences of the patient's caregiver. Treatment should be undertaken as soon as is practicable and, generally, should not be delayed beyond 72 hours following diagnosis.

- Approval of Eylea for ROP was based on data from two randomized, global, Phase III trials, FIREFLEYE (n = 113) and BUTTERFLEYE (n = 120), which compared Eylea to laser photocoagulation in infants with ROP. Patients had to have a maximum gestational age of 32 weeks or a maximum birth weight of 1500 grams. They also had to weigh greater than 800 grams on the day of treatment. Patients also had to meet criteria for type I ROP. Eylea did not meet the goal of noninferiority to laser treatment at 52 weeks in either trial, although about 80% of infants treated with Eylea achieved an absence of active ROP in each trial.

- For patients who fail to achieve ROP regression with the initial therapy and for those in whom vision-threatening ROP recurs, further therapy generally consists of a second treatment using either the same modality or a different modality. Some studies have reported recurrence in as many as one-quarter of treated patients. Reported recurrence rates vary considerably depending on the timing of treatment, the laser treatment technique, the specific anti-VEGF agent and dose used, and/or the definition used to identify recurrence. Patients should meet the type I RO definition to be considered for retreatment.

References:

1. Eylea [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; December 2023.
2. Eylea HD [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; December 2023.
3. Avastin [prescribing information]. South San Francisco, CA: Genentech, Inc.; January 2021.
4. Yesafili [prescribing information]. Cambridge, MA: Biocon Biologics Inc.; May 2024.
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Policy History		
#	Date	Change Description
2.0	Effective Date: 2/12/2026	Annual review of criteria was performed, no changes were made
1.9	Effective Date: 12/04/2025	Updated to include Eydenzelt
1.8	Effective Date: 10/09/2025	Updated to include aflibercept-yszy
1.7	Effective Date: 10/03/2024	Updated to add Enzeevu and Pavblu
1.6	Effective Date: 08/08/2024	Updated to add Ahzantive, Opuviz, and Yesafili and the statement that biosimilars will be approved for all indications of the innovator product when criteria is met
1.5	Effective Date: 02/08/2024	Updated to remove the step through Vabysmo on Eylea HD for the Medicare line of business
1.4	Effective Date: 10/12/2023	Updated to add Eylea HD and a step through Eylea and/or Vabysmo prior to the use of Eylea HD when using every 8-week dosing for Medicare. The name of the policy was changed from Eylea to Aflibercept.
1.3	Effective Date: 06/08/2023	Updated to not require step through Byooviz for all indications
1.2	Effective Date: 06/08/2023	Updated to not require step through Byooviz for DME when vision is worse than 20/50
1.1	Effective Date: 04/06/2023	New policy. This policy replaces previously approved criteria that was embedded in the Intravitreal Injections for Retinal Conditions Policy which is being split into individual drug policies and retired. The authorization period was updated from up to 1 year to at least 60 days and up to 1 year, a step through Byooviz was added, and the indication for retinopathy of prematurity was added.
1.0	Effective Date: 01/01/2021	New Policy

Amtagvi™ (lifileucel)
HCPCS: J3590

Background Information:

- Tumor infiltrating lymphocyte (TIL) therapy is a type of treatment the utilizes the body's own immune system to fight cancer. The immune system naturally creates TIL cells that can recognize distinctive markers on the surface of cancer cells and launch an attack. To make TIL therapy, a patient's TIL cells are collected from a portion of their resected tumor and then expanded outside the body before being infused back into the patient. Once the body is resupplied with TIL cancer-fighting immune cells, tumor cells are attacked and killed.

- TIL therapy has not been studied when given following prior treatment with any TIL therapy or following any other genetically-modified TIL therapy.

- Due to the risk of treatment-related deaths, prolonged severe cytopenia, severe infection, cardiopulmonary impairment, and kidney impairment, TIL therapy is only allowed to be given at certified inpatient treatment centers. The labeling requires patients be monitored for side effects in an intensive care facility and that specialists be available.

- Amtagvi is a tumor-derived autologous T-cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

- Safety and efficacy were established in the C-144-01 trial, a phase II, open-label, single-arm, multicenter study in patients with advanced melanoma who had progressed following a PD-1 inhibitor and BRAF ± MEK targeted agents if indicated. The primary efficacy analysis set included 82 patients who received Amtagvi, among these, 9 patients received Amtagvi at a dose less than 7.5×10^9 viable cells and did not achieve an objective response. Amtgavi was produced from harvested tumor specimens with an average manufacturing time of 23 days and median time to infusion of 34 days. Patients received a non-myeloablative lymphodepletion regimen, a single infusion of Amtagvi, and up to six doses of high-dose interleukin-2. The study excluded patients with an ECOG score of greater than 1, a creatinine clearance of less than or equal to 40 mL/minute, hemoglobin less than 9.0 g/dL, and left ventricular ejection fraction less than 45%. Patients were also excluded if they had an absolute neutrophil count less than 1000 cells/mm^3, platelet count less than 100,000/mm^3, symptomatic and/or untreated brain metastases, history of another primary malignancy that has not been in remission for at least 3 years prior to consideration of Amtagvi, infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy, a detectable HIV, hepatitis B or C viral load, or any primary immunodeficiency. Patients were required to have at least one measurable, resectable lesion that is a minimum of 1.5 cm in diameter post-resection. The primary endpoints included objective response rate (ORR) and duration of response (DoR). The ORR was 31.5% (95% CI: 21.1, 43.4) with 3 complete responses (CR) and 20 partial responses (PR). The median time to initial response was 1.5 months with the median DoR not reached after 18.6 months.

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Policy History		
#	Date	Change Description
1.2	Effective Date: 04/10/2025	Annual review – no changes to the policy were made at this time
1.1	Effective Date: 04/11/2024	New policy - this criteria replaces previously approved preliminary criteria
1.0	Effective Date: 04/01/2024	New Policy

Amvuttra™® (vutrisiran)
HCPCS: J0225

Background Information:

- Amvuttra is a transthyretin (TTR) silencer indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, and for the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations, and urgent heart failure visits.

- Transthyretin amyloidosis (ATTR) is a progressive, life-threatening disorder characterized by the deposition of amyloid fibrils composed of TTR, a plasma transport protein for thyroxine and vitamin A that is predominantly produced by the liver and to a lesser extent by the choroid plexus and in retinal cells.

- In ATTR, TTR misfolds, causing it to aggregate into amyloid fibrils that accumulate in organs, nerves, and tissues. The buildup of these amyloid deposits results in progressive dysfunction at the site of deposition. Amyloid deposition can occur in the heart, gastrointestinal tract, kidneys, thyroid, salivary glands, eyes, peripheral nervous system, and central nervous system. The phenotype is driven by deposition site and may be predominantly cardiac, neurologic, or mixed.

- There are two types of ATTR: hereditary (hATTR), or variant, which is due to inherited mutations of the TTR gene that cause misfolding of the tetramer subunits, and wild-type, which occurs in the presence of a normal TTR gene, is typically associated with aging, and is most often diagnosed in men 65 years and older. In wild-type ATTR, TTR typically only deposits in the heart and manifests as cardiac symptoms. hATTR, in contrast, may be predominantly neuropathic, cardiomyopathy, or a mixed phenotype characterized by both.

- hATTR with polyneuropathy (hATTR-PN)

- hATTR-PN is the most common neurologic manifestation. Without treatment, patients will have progressive neuropathy and disability ultimately resulting in death within 10-15 years of disease onset.

- Patients with hATTR-PN may present with peripheral neuropathy (sensory and motor; tingling or increased pain in the hands, feet and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking), autonomic neuropathy (e.g., orthostasis, abnormal sweating, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety]), GI impairment, cardiomyopathy, nephropathy, or ocular deposition. Most hATTR-PN cases, however, are classified as neuropathic.

- Amyloid deposition induces a length-dependent peripheral neuropathy beginning in the lower limbs with symptoms like toe discomfort due to numbness and spontaneous pain. Continued aggregation of amyloid on the nerve fibers contributes to sensory loss extending upwards toward the proximal lower limbs as motor deficits and impaired sensations occur. Walking becomes increasingly difficult as balance and gait are affected. Neuropathic pain transitions to a burning sensation worsening at night. Over time, sensory deficit extends to the upper limbs, forearms, fingers and trunk and motor deficit follows with the same length dependent progression. At this stage, potentially life-threatening autonomic dysfunction is present manifesting as orthostatic hypotension, anhidrosis, neurogenic bladder, disturbances of gastrointestinal motility, and sexual impotence.

- Cardiac disease may occur in approximately 50% of patients with hATTR-PN. Ocular involvement is also common, including vitreous opacity, dry eye, glaucoma, and pupillary disorder.

- A rarer presentation of hATTR is leptomeningeal and meningovascular amyloidosis, often with concomitant vitreous opacity (oculoleptomeningeal amyloidosis). Several mutations have reportedly been linked to this type of hATTR, though it may also manifest in more advanced cases of *Val30MET*-mutated hATTR-PN.

- Central nervous system symptoms include stroke, subarachnoid hemorrhage, dementia, ataxia, seizures, and sensorineural hearing loss.

- The source of mutant TTR in (oculo)leptomeningeal and meningovascular amyloidosis is thought to be the choroid plexus and retinal cells versus the liver. As such, ocular and meningovascular manifestations are commonly seen after liver transplantation because the source of mutant TTR is left unaffected.

- To date, no treatments have been proven to be beneficial for the treatment of (oculo)leptomeningeal and meningovascular amyloidosis.

- The 2013 guideline of transthyretin-related hereditary amyloidosis for clinicians recommends that the most reliable diagnostic approach involves genetic testing and tissue biopsy to confirm the presence of active amyloid formation. Genetic testing is needed to document the TTR gene mutations; if testing is normal, a diagnosis of hATTR is excluded.

- Options for hATTR-PN treatment are limited. Treatment strategies include removing the source of mutant TTR, inhibiting TTR formation, stabilizing the TTR molecule, and therapy directed at removing the amyloid deposits. Regardless of the choice of treatment, the 2013 guidelines and published expert opinion from 2024 recommend treatment initiation as soon as possible after diagnosis to slow or halt disease progression. The best outcomes have been shown in patients diagnosed at younger ages and/or without advanced disease.

- For hATTR-PN, our best treatment option historically had been orthoptic liver transplant, which removes the source of mutant TTR and was considered the gold standard for hATTR-PN treatment early in the course of disease. In hATTR-PN, the liver is the primary source of mutant TTR; transplantation eliminates approximately 95% of the production of mutant TTR and may slow or halt disease progression outside of the brain and/or eyes, though nerve function rarely improves post-transplant. Transplant does not effectively prevent cardiomyopathy, however, and is not recommended for patients with late stage hATTR-PN or leptomeningeal disease. With later stages of hATTR-PN and cardiomyopathy, there are concerns of disease progression due to deposition of wild-type TTR from the transplanted liver on the preexisting amyloid from the variant TTR

- Numerous disease-modifying therapeutics are now available for hATTR-PN, including Amvuttra (vutrisiran), Onpattro® (patisiran), and Wainua® (eplontersen). Guidelines have not yet been updated to include Amvuttra, Onpattro, Tegsedi, and Wainua specifically; however, they do note that early detection is critical and patients with early-stage disease should be treated with any approved drugs as they become available and as the patient's disease state meets drug indications, independent of liver transplant plans.

- Amvuttra, Onpattro, Tegsedi, and Wainua are FDA-approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Wainua is FDA approved to be administered by the patient or caregiver, while a healthcare provider is required for Amvuttra and Onpattro administration per approved labeling. To date, there is no literature supporting the use of one product over another, nor is there support for the use of any of these products together or in combination with other therapies approved for ATTR. The 2024 expert opinion does not offer recommendations on choice of specific treatment due to the lack of direct comparison trials and advises that clinicians consider the efficacy and safety considerations, in addition to any comorbidities and personal preferences around ease of use for an individual patient.

- Amvuttra is a small interfering ribonucleic acid agent (siRNA) targeting TTR that silences a portion of RNA involved in causing the disease. Amvuttra is designed to deliver the drug directly into the liver to interfere with RNA production of an abnormal form of TTR, ultimately reducing accumulation of amyloid deposits in peripheral nerves.

- In the pivotal phase 3 HELIOS-A trial, Amvuttra demonstrated better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, numbness), reflexes and autonomic symptoms (blood pressure, heart rate, digestion) compared to an external placebo group from patisiran's pivotal APOLLO trial. Amvuttra-treated patients also scored better on assessments of walking, nutritional status, and the ability to perform activities of daily living. Amvuttra also demonstrated non-inferiority in serum TTR reduction relative to the within-study patisiran reference group, which showed results consistent to the Amvrutta-treated group throughout the study.

- In clinical trials, Amvuttra was only evaluated in patients with a baseline polyneuropathy disability (PND) score $\leq$IIIb, which equates to a familial amyloidotic polyneuropathy (FAP) stage of 1 or 2. The PND score (range 0-IV) stages disease based on walking ability, while the FAP stage (stage 0-3) assesses the patient's level of ambulation and the severity/progression of neuropathy. Amvuttra was not evaluated in patients with baseline

PND score of IV which, like FAP stage 3, designates patients with late-stage, significantly advanced disease who are wheelchair-bound or bedridden, therefore clinical trials do not support use in this patient population with advanced disease.

- Patients who received prior TTR-lowering treatment and those with a history of liver transplant were also excluded from clinical trials of Amvuttra. There is no literature to support that patients who received a liver transplant would experience benefit from treatment with Amvuttra as they would not be expected to produce mutated TTR post-transplant.

- ATTR with cardiomyopathy (ATTR-CM)

- Patients with ATTR-CM are typically males aged 65 years or older. The condition may be inherited or occur sporadically sans inheritance pattern due to wild-type (or normal) TTR.

- In ATTR-CM, the left ventricle ejection fraction is normal or only mildly reduced and coupled with ventricular hypertrophy. Amyloid deposition commonly affects the conduction system as well, leading to bundle branch block and on occasion atrioventricular and sinoatrial block. Pacemaker implantation is often required. Typical signs and symptoms include dyspnea, lower extremity edema, elevated jugular venous pressure, hepatic congestion, and ascites. In more advanced disease, signs and symptoms of low cardiac output may also occur (e.g., diminished pulse pressure and capillary refill). ATTR-CM progresses rapidly, with a life expectancy of 3 to 5 years from diagnosis, depending on the subtype.

- Clinical suspicion for cardiac amyloidosis includes left ventricular wall thickening (thickness > 14 mm) in conjunction with fatigue, dyspnea, or edema, especially in the context of discordance between wall thickness on echocardiogram and ECG voltage, and in the context of aortic stenosis, heart failure with preserved ejection fraction (HFpEF), carpal tunnel syndrome, spinal stenosis, and autonomic or sensory polyneuropathy.

- The 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guideline for the management of heart failure and the 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient with Cardiac Amyloidosis provide the most up to date recommendations for the diagnosis and treatment of patients with cardiac amyloidosis.

- In patients with the above features, it is important to differentiate between amyloid light chain cardiomyopathy (AL-CM) and ATTR-CM. Per both guidelines, this is done by screening for the presence of serum and urine monoclonal light chains. AL-CM can be ruled out by obtaining a monoclonal light chain screen assessing serum free light chain (sFLC) concentration and serum and urine immunofixation electrophoresis (IFE). If no monoclonal light chains are detected then AL-CM is excluded and technetium-labeled bone scintigraphy is performed to confirm the presence of ATTR-CM. Scans may be positive even in AL-CM; therefore, a bone scintigraphy scan alone cannot distinguish ATTR-CM from AL-CM without concomitant light-chain testing.

- Endomyocardial biopsy is an additional, though more invasive, option for diagnosis and is recommended in situations where there is high clinical suspicion of ATTR-CM in patients with abnormal monoclonal light chain screening, high clinical suspicion of ATTR-CM in patients with negative or questionable scintigraphy results, or in the event cardiac scintigraphy is not available. Amyloid deposits detected on biopsy are then identified, or typed, by mass spectrometry, immunoelectron microscopy or immunohistochemistry to determine whether the precursor protein is TTR.

- If ATTR-CM is identified, genetic sequencing of the TTR gene is performed to determine if the patient has hereditary or wild-type disease. This differentiation is important in triggering genetic counseling, screening family members, and potentially identifying appropriate pharmacologic therapies.

- For patients with ATTR-CM, hereditary or wild-type, and exhibiting NYHA class I-III symptoms, the 2022 guidelines recommend treatment with tafamidis. Tafamidis is approved under the brand names Vyndaqel® and Vyndamax® for the treatment of adults with ATTR-CM to reduce cardiovascular mortality and cardiovascular-related hospitalization. It works by stabilizing TTR to prevent it from misfolding and subsequently creating amyloid deposits. It should be noted that tafamidis prevents but does not reverse amyloid deposition; therefore, its greatest benefit is anticipated when administered early in the disease course. The 2023 ACC consensus statement aligns with the 2022 guidelines, recommending that tafamidis remain the first-line agent to treat ATTR-CM as at the time of publication it was the only available FDA approved drug for this indication.

- In December 2024, the FDA approved Attruby (acoramidis) for the treatment of wild-type or variant ATTR-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization. Attruby is a transthyretin stabilizer like tafamidis. Though it boasts a near-complete (> 90%) stabilization of TTR, the clinical significance of this finding is uncertain as there is insufficient evidence associating TTR levels and degree of stabilization with improved clinical outcomes. Amvuttra is the third agent approved for ATTR-CM and has a novel mechanism of action in this category, inhibiting hepatic synthesis of both wild-type and variant TTR mRNA at the source to prevent the protein from forming in the first place. Guidelines have not yet been updated to include either Attruby or Amvuttra.

- In the pivotal Phase III HELIOS-B clinical trial, 645 patients with either wild-type or hereditary ATTR-CM and a history of heart failure (NYHA Class I-III) received either Amvuttra or placebo once every 3 months for up to 36 months. Patients with NYHA Class IV or high-risk Class III (i.e., NT-proBNP level>3,000 pg/mL and eGFR <45 mL/min/1.73m^2 of body-surface area), or a PND of IIIa, IIIb, or IV (indicating a cane or stick is needed to walk, or that a patient is wheelchair-bound) were excluded. At baseline, 40% of patients were established on tafamidis, and participants were permitted to initiate open-label tafamidis during the study. Treatment with Amvuttra led to significant reduction in the risk of all-cause mortality and recurrent cardiovascular events compared to placebo in the overall and monotherapy populations of 28% and 33%, respectively.

- Though HELIOS-B represents the most robust data currently available on concurrent TTR silencer and TTR stabilizer use, the trial was not designed to determine the differences between monotherapy and combination therapy. Therefore, there is insufficient evidence to distinguish the net health benefit among the drugs when used as monotherapy or to support the use of combination therapy in ATTR-CM. Additionally, there is no literature to date supporting the use of Amvuttra in combination with other therapies approved for ATTR, such as Onpattro, Wainua, or Attruby.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 06/05/2025	Added criteria for new ATTR-CM indication Reworded diagnosis criteria for clarity to align with approved labeling Removed hATTR-PN criteria preventing use with NYHA class >2 since Amvuttra can now be used for cardiomyopathy in patients beyond class 2 Removed criteria preventing use with previous liver transplant to align with management for other ATTR therapies
1.2	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 08/10/2023	Annual review of criteria performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Anktiva® (nogapendekin alfa inbakicept-pmln)
HCPCS: J9028

Background Information:

- Bladder cancer is one of the more common forms of cancer. Approximately 75% - 80% of newly diagnosed bladder cancers are classified as NMIBC – a type of cancer that has grown through the lining of the bladder but hasn't yet invaded the muscle layer. This type of cancer is associated with high rates of recurrence (between 30 to 80%) and the risk of progression to invasive and metastatic disease.
- Treatment and care of patients with high-risk NMIBC, including those with CIS, often involves removing the tumor followed by BCG bladder instillation therapy to reduce the risk of recurrence. Few effective treatment options exist for patients who develop BCG-unresponsive disease. The failure to achieve a complete response, or the disappearance of all signs of cancer as seen on cystoscopy, biopsied tissue, and urine, is associated with an increased risk of death or a disease-worsening event.
- Anktiva is an interleukin-15 (IL-15) receptor agonist indicated with BCG for the treatment of adult patients with BCG-unresponsive nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.
- The 2025 National Comprehensive Cancer Network Bladder Cancer Treatment Guidelines recommend TURBT for staging followed by a single dose of intravesicular mitomycin or gemcitabine as the first step in treatment. Following the tumor evaluation, if the tumor is considered high-grade, BCG is the preferred adjuvant therapy and intravesicular mitomycin or gemcitabine provide additional options to those who aren't candidates for BCG therapy. BCG is typically given weekly for 6 weeks at induction followed by maintenance of 3 weekly instillations at month 3, 6, 12, 18, 24, 30, and 36. Two 6-week BCG induction courses should be completed before the patient is considered non-responsive to the therapy. If patients have had recurrence or are considered non-responsive to BCG therapy, cystectomy, Keytruda®, or Adstiladrin® are currently recommended as second-line therapies.
- Safety and efficacy were evaluated in QUILT-3.032 trial, a single-arm, multicenter trial in 77 adults with BCG-unresponsive, high-risk, NMIBC with CIS with or without Ta/T1 papillary disease following transurethral resection. BCG-unresponsive high-risk NMIBC was defined as persistent or recurrent CIS within 12 months of receiving adequate BCG therapy, recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy, or T1 high-grade disease at the first evaluation following an induction BCG course alone. Adequate BCG was defined as the administration of at least five of six doses of an initial induction course plus either at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. If patients experienced failure of BCG therapy during induction, they must have gotten at least 5 of six doses of the initial induction course. Patients were excluded from the trial if they had an ECOG score greater than 2 or had concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra. All visible papillary tumors were resected and those with persistent T1 disease on TURBT should undergo an additional re-TURBT prior to beginning therapy. Patients received 400 mcg Anktiva with BCG weekly for 6 consecutive weeks during the induction treatment period and then once a week every 3 weeks at 4, 7, 10, 13, and 19 months for patients with no or low grade disease. Patients with persistent CIS or high grade Ta disease at 3 months were eligible to receive a second induction course. Patients with ongoing complete response at 25 months were eligible to receive

additional instillations once a week every 3 weeks at months 25, 31, and 37. Overall, 62% of subjects experienced a complete response rate with 58% having a response lasting for at least a year and 40% for at least two years.

References:

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Policy History		
#	Date	Change Description
1.0	Effective Date: 09/01/2025	New Policy

Arcalyst® (rilonacept)
HCPCS: J2793

Background Information:

- Arcalyst is an interleukin(IL)-1β blocker indicated for the treatment of
- Adults and children 12 years of age and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)
- Maintenance of remission of deficiency of interleukin-1 receptor antagonist (DIRA) in adults and pediatric patients weighing at least 10 kg
- Treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years and older
- Cryopyrin-Associated Periodic Syndromes
- CAPS are a group of rare genetic diseases affecting approximately 200 to 300 people in the United States, attributed to a specific genetic mutation. There are two types of CAPS recognized that affect the majority of patients.
  - FCAS patients have recurrent intermittent episodes of fever and rash that primarily follow natural, artificial (e.g., air conditioning), or both types of generalized cold exposure.
  - MWS patients have chronic fever and rash that may wax and wane in intensity. Symptoms are sometimes exacerbated by generalized cold exposure. This syndrome may be associated with deafness or amyloidosis.
    - The diagnosis of CAPS is confirmed by genetic testing for NALP3 mutations, however, in some patients, the mutation is not detectable for various reasons. In patients with no detectable NALP3 mutations, diagnostic criteria include raised inflammatory markers (C-reactive protein [CRP] and serum amyloid A) plus at least two of six typical CAPS manifestations which include urticaria-like rash, cold-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis, and skeletal abnormalities.
  - Ilaris® (canakinumab) is another IL-1β blocker indicated for the treatment of CAPS. Both products appear to have similar efficacy. Ilaris has a more convenient dosing regimen and is indicated for a younger age population (4 years old).
  - Deficiency of Interleukin-1 Receptor Antagonist
  - DIRA is a very rare genetic autoinflammatory syndrome that presents in the first days of life. The distinctive features are inflammatory changes in the skin and bone in the absence of fever. All affected children develop a pustular rash in which there may be discrete crops of pustules or a severe generalized pustular eruption that may resemble generalized pustular psoriasis. All patients will also develop inflammation in the bones, which causes painful movement, joint swelling, and characteristic changes on x-ray. Patients may also present with fetal distress, mouth lesions, hepatosplenomegaly, generalized ichthyosis-like changes, pitting and separation of the nail from the nail bed, stomatitis, and conjunctivitis. If left untreated, patients may die of multisystem organ failure.
  - Diagnosis of DIRA is confirmed through genetic testing for IL1RN mutations. DIRA is an autosomal recessive anti-inflammatory disease and therefore, patients should have two mutations of the IL1RM gene to exhibit symptoms. The double mutation causes an absence of interleukin-1–receptor antagonist allowing unopposed action of interleukin-1 resulting in systemic inflammation with skin and bone involvement.

- Kineret has been used as a first-line agent for the treatment of DIRA since the disease's discovery and can be used for induction and maintenance of remission. Arcalyst has only been studied to maintain remission following induction with Kineret. There are no head to head trials to show Arcalyst is superior to Kineret once remission is reached, as such, since patients must start therapy with Kineret, it is reasonable to continue therapy with it unless an adverse reaction or contraindication is experienced.
- Recurrent Pericarditis
- Recurrent pericarditis refers to a syndrome in which acute pericarditis recurs after the agent inciting the original acute attack has disappeared or has ceased to be active. It is diagnosed with a documented first episode of acute pericarditis, a symptom-free interval of 4 – 6 weeks or longer, and evidence of subsequent recurrence of pericarditis, such as: chest pain, pericardial rub, fever, electocardiogarm changes, new or worsening pericardial effusion, and/or elevated markers of inflammation. The recurrence rate after an initial episode of pericarditis ranges from 15% to 30%.
- The 2015 European Society of Cardiology Guidelines for the Diagnosis and Management of Pericardial Diseases recommend therapy be targeted at the underlying etiology in patients with an identified cause with aspirin or NSAIDs remaining the mainstay of therapy. Colchicine is recommended on top of standard anti-inflammatory therapy to improve the therapeutic response, improve remission rates, and prevent recurrences.
- In cases of incomplete response to aspirin/NSAIDs and colchicine, treatment guidelines state corticosteroids may be used, but they should be added at low to moderate doses to aspirin/NSAIDs and colchicine as triple therapy. Corticosteroids should not replace these other therapies and should be used to achieve better control of symptoms. Corticosteroids at low to moderate doses should be avoided if infections cannot be excluded and should be restricted to patients with specific indications, such as, systemic inflammatory diseases, post-pericardiotomy syndromes, or pregnancy, or those with NSAID contraindications. Although corticosteroids provide rapid control of symptoms, they favor chronicity, more recurrences, and side effects. If corticosteroids are used, they should be tapered slowly. A critical threshold for recurrences is a 10 – 15 mg/day dose of prednisone or equivalent. In cases of recurrence, every effort should be made not to increase the dose or to reinstate corticosteroids.
- After obtaining a complete response, tapering should be done with a single class of drug at a time before colchicine is gradually discontinued. Recurrences are possible after discontinuation of each drug. Each tapering should be attempted only if symptoms are absent and C-reactive protein (CRP) is normal.
- Kineret has been shown to reduce the risk of further recurrences in patients with recurrent pericarditis. In the AIRTRIP trial, 21 patients with at least three episodes of recurrent pericarditis were treated with Kineret for two months. After two months, and following resolution of pericarditis symptoms, patients were randomized in a double-blind fashion to continue Kineret or switch to placebo for six months or until symptoms recurred. After a median follow-up of 14 months, patients in the Kineret group had significantly fewer recurrences (18% versus 90%) and greater symptom-free survival compared with patients receiving placebo. Patients treated with Kineret were able to wean off of corticosteroids.
- Safety and efficacy of Arcalyst was established in the RHAPSODY trial, a Phase III, double-blind, placebo-controlled, randomized withdrawal study of 86 patients with symptomatic pericarditis recurrence. Patients were included if they were presenting with at least their third episode of pericarditis at screening and had been on stable doses of aspirin/NSAIDs, colchicine, and/or glucocorticoids for at least 3 days prior to Arcalyst administration. Patients were excluded if they pericarditis secondary to tuberculosis, post-thoracic blunt trauma, myocarditis, systemic

autoimmune diseases, or neoplastic, purulent, or radiation etiologies. The primary efficacy endpoint was time to first adjudicated pericarditis recurrence based on pain, CRP and clinical signs in the event-driven withdrawal period. Of the 61 subjects randomized, 23 (74%) in the placebo arm had a recurrence compared with 2 (7%) in the rilonacept arm who temporarily discontinued treatment for 1 – 3 doses. The median time-to-recurrence on rilonacept could not be estimated because too few events occurred and was 8.6 weeks (95% CI 4.0, 11.7) on placebo with a hazard ratio of 0.04 ($p < 0.0001$). The median time to treatment response was 5 days with a 97% treatment response rate. In addition, patients receiving Arcalyst had a 96% reduction in the risk of a recurrent pericarditis event.

- Arcalyst and Kineret are IL-1 inhibitors that have been studied in the treatment of recurrent pericarditis. Guidelines do not recommend the use of one agent over another and there are no head to head trials comparing the efficacy of Arcalyst and Kineret for the indication; therefore, use of Kineret provides the best value.
- Arcalyst has not been studied in combination with other biologic medications, such as Kineret, for use in recurrent pericarditis. Due to lack of evidence for combination use, Arcalyst should not be used in combination with other biologics for recurrent pericarditis.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 10/03/2024	Removed criteria preventing combination use with other biologic medications used for recurrent pericarditis, such as, Kineret and added "Not to be used in combination with other biologics or targeted DMARDs for the same indication" criteria
1.2	Effective Date: 06/06/2024	Updated to include criteria not allowing use with other biologic agents for recurrent pericarditis
1.1	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Atezolizumab Products
Tecentriq® (atezolizumab) J9022
Tecentriq Hybreza™ (atezolizumab and hyaluronidase-tqjs) J9024

Background Information:

- Tecentriq and Tecentriq Hybreza are a programmed death receptor-1 (PD-L1)-blocking antibodies indicated for the following:
- As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test
- For the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations
- In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
- In combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
- For the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving Tecentriq.
- In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)
- In combination with bevacizumab for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy
- In combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma
- For the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS)
- The National Comprehensive Cancer Network (NCCN) guidelines category 1 and 2A recommendations are based on uniform NCCN consensus that the recommendations are appropriate. Treatment regimens have been studied and shown to be efficacious when administered as listed in the guidelines. Category 2B and 3 recommendations do not have a high level of evidence to support use and also do not have a uniform consensus from the NCCN panel that the recommendations are appropriate.
  - There are no studies to support use of Tecentriq or Tecentriq Hybreza following failure. NCCN treatment guidelines also do not recommend use of Tecentriq, Tecentriq Hybreza, or other PD-L1 checkpoint inhibitors following a previous failure.
  - Tecentriq and Tecentriq Hybreza have not been studied in patients on chronic immunosuppressant therapy and therefore, should not be used in patients on chronic immunosuppressants.

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Policy History		
#	Date	Change Description
1.7	P&T Date: 06/05/2025 Effective Date: 07/21/2025	Updated to only allow 24 months of therapy for metastatic non-small cell lung cancer and added the trial and failure of preferred products statement

1.6	Effective Date: 10/03/2024	Updated to include Tecentriq Hybreza. The name of the policy was changed from Tecentriq to Atezolizumab Products.
1.5	Effective Date: 02/08/2024	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 02/02/2023	Updated approval length to allow for FDA recommended dosing for at least 60 days and up to 6 months at a time
1.3	Effective Date: 02/10/2022	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 02/04/2021	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 01/01/2021	New Policy

Aucatzyl® (obecabtagene autoleucel)
HCPCS: Q2058

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.
- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.
    - Aucatzyl is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
- Safety and efficacy for use in acute lymphoblastic leukemia were established in the FELIX trial, a multicenter, phase II trial of 112 adult patients with relapsed or refractory ALL. If patients were Philadelphia chromosome positive they had to be intolerant to a tyrosine kinase inhibitor (TKI), had failed 2 previous lines of treatment with any TKI or 1 line of a second-generation TKI, or had a contraindication to a TKI. Patients with prior allogeneic SCT within 100 days of therapy, any active central nervous system malignancy, ECOG performance status of 2 or greater, or active serious infection were excluded. The primary end point was complete response (CR) and CR with incomplete count recovery (CRi). Secondary end points included event-free survival, overall survival (OS), safety, and duration of response (DOR). Of the 65 patients evaluable for efficacy, 27 patients (42%; 95% CI: 29%, 54%) achieved CR within 3 months. The median duration of CR achieved within 3 months was 14.1 months (95% CI: 6.1, not reached).
    - Use of Aucatzyl required adequate kidney function. Other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other CAR-T therapies support their use in these patients, Aucatzyl should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 ml/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.
    - Use of Aucatzyl requires adequate liver function. Other CAR-T therapies have been studied in subjects with an alanine aminotransferase of up to 5 times the ULN and the CTCAE recommendations have set 5 times the ULN as the cutoff for grade 2 adverse reactions. As the classification system uses 5 times the ULN and other CAR-T therapies have data supporting use in this patient population, Aucatzyl should be tolerated in these patients as well. As there is no data to support administration of CAR-T at levels higher than 5 times the ULN, therapy should not be given to patients not meeting that threshold.
    - The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. There is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Aucatzyl should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.

- Provider portal platforms allow the capture of clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

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Policy History		
#	Date	Change Description
1.2	Effective Date: 12/04/2025	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 12/12/2024	New policy - this criteria replaces previously approved preliminary criteria
1.0	Effective Date: 11/25/2024	New Policy

Benlysta® (belimumab)
HCPCS: J0490

Background Information:

- Benlysta is indicated for the treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy and adult patients with active lupus nephritis who are receiving standard therapy.
- The efficacy of Benlysta has not been evaluated in patients with severe active central nervous system lupus. Severe active central nervous system lupus was defined as seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis, or CNS vasculitis requiring therapeutic intervention within the previous 60 days before initiation of Benlysta in the clinical trials. Use of Benlysta in patients with this condition is not recommended.
- Use of Benlysta also has not been studied in combination with other biologics and is not recommended.
- Seropositivity was defined in the clinical trials by 2 positive ANA titers (≥ 1:80) or anti-dsDNA antibodies (≥ 30 IU/mL) on different days. The 2019 EULAR/ACR classification system for SLE allow ANA levels to be used as a qualifier for SLE, however, because ANA can elevate transiently and also be a marker for other diagnoses, a second confirmatory test must be done to confirm seropositivity. While other classification systems exist to define lupus, these systems do not ensure patients are seropositive as they only have to meet a certain number of criterion for diagnosis. Those criterion may or may not include positive tests for elevated ANA or anti-dsDNA titers.
- Both the intravenous and subcutaneous formulation of Benlysta were studied in phase III, multicenter, randomized, placebo-controlled trials of patients with active, autoantibody-positive SLE. The intravenous formulations were assessed in the BLISS-76 and BLISS-52 trials and the subcutaneous formulation in the BLISS-SC trial. All trials included seropositive patients who were stable and maintained on standard therapy throughout the study. People with severe lupus nephritis or severe CNS lupus were excluded. Subjects were required to have a SELENA-SLEDAI score greater than 6 in the intravenous trials and greater than 8 in the subcutaneous trials. All studies primary endpoints were the SLE Responder Index (SRI4) response rate at week 52. The SRI4 is a composite index requiring a 4-point reduction in the SELENA–SLEDAI score, no worsening (increase from baseline) in the physician's global assessment (on a 0 – 10-cm visual analog scale), and no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores at week 52 compared with baseline. In all studies, the Benlysta treatment arms showed statistical significance versus placebo for the primary endpoint.
- The use of Benlysta in patients with active lupus nephritis was studied in the BLISS-LN trial, a phase III, multinational, multicenter, randomized, double-blind, placebo-controlled study of 448 patients. The trial included seropositive patients who were stable and maintained on standard therapy throughout the study. Patients had biopsy proven lupus nephritis showing active lesions prior to study entry. Patients with a GFR of less than 30 ml/min/1.73 m^2 of body surface area (BSA) were excluded. The study met its primary endpoint demonstrating that a statistically significant greater number of patients achieved primary efficacy renal response (PERR) at 104 weeks when treated with Benlysta plus standard therapy compared to placebo plus standard therapy (43% vs 32%, odds ratio (95%

CI) 1.55 (1.04, 2.32), p-value = 0.0311). Statistical significance compared to placebo across all four major secondary endpoints was achieved, including complete renal response and time to renal-related event or death. The safety results are consistent with the known safety profile of Benlysta.

- The 2020 EULAR guidelines recommend kidney biopsy for SLE patients showing any sign of kidney involvement including glomerular hematuria and/or cellular casts, proteinuria greater than 0.5 g/24 hours, spot urine protein-to-creatine ratio (UPCR) greater than 500 mg/g, or unexplained decrease in glomerular filtration rate. The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification still represents the gold standard for assessment of kidney biopsy in LN. Patients with class III focal lupus nephritis, class IV diffuse lupus nephritis with or without coexisting class V membranous lupus nephritis, or pure class V lupus nephritis were included in the BLISS-LN trial.
- The 2020 EULAR guidelines recommend use of hydroxychloroquine in all patients with the use of glucocorticoids to treat flares. The goal of therapy is for patients to get into remission or a state of low disease activity. If hydroxychloroquine use is still resulting in disease flare, use of immunosuppressants should be considered. The guidelines state Benlysta should be considered in patients who have failed hydroxychloroquine in combination with glucocorticoids and immunosuppressants.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Beovu® (brolucizumab-dbll)
HCPCS: J0179

Background Information:

- Intravitreal injections of anti-vascular endothelial growth factor (VEGF) have been widely used by ophthalmologists to treat a variety of ocular diseases. They are injected directly into the eye to prevent the formation of new blood vessels and reduce blood vessel leakage and inflammation. Beovu is an anti-VEGF currently indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME).
- Age-related Macular Degeneration
- Age-related macular degeneration is a degenerative disease of the macula that results primarily in loss of central vision. Wet AMD is characterized by growth of abnormal vessels into the subretinal space. These abnormal blood vessels leak leading to collections of subretinal fluid and/or blood beneath the retina. The 2022 American Academy of Ophthalmologists (AAO) Age-Related Macular Degeneration Preferred Practice Pattern Guidelines recommend observation and early detection, antioxidant vitamin and mineral supplements, and intravitreal injections of anti-VEGF agents for the management of wet AMD. Guidelines recommend Eylea™, Avastin®, Vabysmo™, or Lucentis for treatment. The guidelines have not been updated with Beovu®, Byooviz, and Susvimo.
- Diabetic Macular Edema
- Diabetic retinopathy and DME are common complications and the ocular manifestations of end-organ damage in diabetes mellitus. The 2022 AAO Diabetic Retinopathy Preferred Practice Pattern Guidelines state the goals of therapy for DR and DME include improvement or stabilization of visual function, improvement in vision-related quality of life, and optimal control of blood glucose, blood pressure, and other metabolic risk factors. Patients should always be treated with anti-VEGF therapy if they have severe non-proliferative DR or proliferative DR with center-involved macular edema. In cases of mild to moderate non-proliferative DR with center-involved macular edema, patients should also receive intravitreal injections. The guidelines support the use of Lucentis, Eylea, Vabysmo, and Avastin. AAO recommendations were based on trials comparing Eylea, Avastin, and Lucentis to focal laser treatment. All trials showed that treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years compared to laser treatment.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 04/06/2023	New policy. This policy replaces previously approved criteria that was embedded in the Intravitreal Injections for Retinal Conditions Policy which is being split into individual drug policies and retired. The authorization period for Beovu was updated from up to 1 year to at least 60 days and up to 1 year
1.0	Effective Date: 01/01/2021	New Policy

Bevacizumab Policy

Alymsys® (bevacizumab-maly) Q5126
Avastin® (bevacizumab) J9035
Avzivi® (bevacizumab-tnjn) J3590
Jobevne™ (bevacizumab-nwgd) J9035
Mvasi™ (bevacizumab-awwb) Q5107
Vegzelma® (bevacizumab-adcd) Q5129
Zirabev™ (bevacizumab-bvzr) Q5118

Background Information:

- Bevacizumab and its biosimilars are monoclonal antibodies that bind to and inhibit the activity of vascular endothelial growth factor (VEGF). Bevacizumab is approved for the following indications:
- In combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment of patients with metastatic colorectal cancer (mCRC)
- In combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment of patients with mCRC who have progressed on a first-line bevacizumab-containing regimen
- In combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC)
- The treatment of recurrent glioblastoma (GBM) in adults
- In combination with interferon alfa for the treatment of metastatic renal cell carcinoma (mRCC)
- In combination with paclitaxel and cisplatin or paclitaxel and topotecan for the treatment of patients with persistent, recurrent, or metastatic cervical cancer
- In combination with carboplatin and paclitaxel followed by bevacizumab as a single agent for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection
- In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan 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
- In combination with carboplatin and paclitaxel or with carboplatin and gemcitabine followed by bevacizumab as a single agent for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
- In combination with atezolizumab for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy
- While not specifically indicated for ocular conditions, bevacizumab has been used off-label for years to treat multiple eye disorders including macular degeneration, macular edema, and diabetic retinopathy. Bevacizumab has the same mechanism of action as the other therapies for these diseases and its use is guideline supported.

- NCCN guidelines state an FDA approved biosimilar can be substituted for Avastin. The guidelines do not specify what biosimilars are appropriate for a specific tumor type which allows for use of any of the biosimilars to be used for any indication the innovator product is FDA approved for.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 06/05/2025	Updated to include Jobevne
1.3	Effective Date: 02/13/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 02/08/2024	Updated to include Avzivi
1.0	Effective Date: 01/01/2024	New Policy

Bimzelx® (bimekizumab-bkzx)
HCPCS: J3590; C9399

Background Information:

- Bimzelx is an interleukin (IL)-17A and IL-17F inhibitor approved to treat:
- Moderate to severe plaque psoriasis (PsO) in adults who are candidates for systemic therapy or phototherapy.
- Adults with active psoriatic arthritis (PsA)
- Adults with active non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation
- Adults with active ankylosing spondylitis (AS)
- Adults with moderate to severe hidradenitis suppurativa (HS)
- Other drugs in this class (Cosentyx®, Taltz®, Siliq®) only target IL-17A.
- Psoriasis
- PsO is a chronic, painful and life-altering immune-mediated disease which predominantly manifests with skin and joint involvement. Patients may also experience significant cardiovascular and psychological comorbidities. Approximately 2% of U.S. adults are affected by psoriasis (men and women equally), and it can occur at any age. Approximately 90% of psoriasis-affected patients have plaque psoriasis, which is characterized by well-defined round or oval plaques that vary in size and often coalesce. The severity of psoriasis is defined as: mild = less than 3% of body affected; moderate = 3-10% of body affected; and severe being more than 10% of the body affected.
- Per the 2020 Joint American Academy of Dermatology - National Psoriasis Foundation (AAD-NPF) guidelines of care for the management and treatment of PsO with topical therapy and alternative medicine modalities for PsO severity measures: topical corticosteroids provide a high efficacy and good safety option for patients with localized disease. They are generally recommended as first-line therapy. Choice of steroid potency may depend on severity, location, patient preference, and patient age, while the duration of treatment may vary with steroid potency, location and severity of disease often ranging from 2-12 weeks. Therapeutic regimens may include 2-4 weeks with a topical steroid applied twice daily, followed by a maintenance regimen where topical steroids are alternated with a steroid-sparing topical agent. Treatment with topical steroids for over 12 weeks is recommended under careful supervision by a physician.
- Per the 2019 Joint AAD-NPF Foundation guidelines of care for the management and treatment of PsO with phototherapy: phototherapy serves as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications or simply seeking an adjunct to a failing regimen. Guidelines also state that the majority of patients with mild-to-moderate disease have adequate disease control with topical therapies and phototherapy alone.
- Per the 2020 Joint AAD-NPF guidelines of care for the management and treatment of PsO with systemic nonbiologic therapies: many oral medications, including methotrexate, cyclosporine, and acitretin, have been used for decades to treat psoriasis, each with its own benefits and risks. Most work by targeting the immune system, whereas others, such as acitretin, work predominantly

by decreasing keratinocyte hyperproliferation, thus restoring the normal epidermal differentiation. Both methotrexate and cyclosporine are category A guideline recommendations for the treatment of moderate to severe PsO in adults and for severe, recalcitrant PsO, respectively. Studies examining the use of methotrexate and cyclosporine in PsO showed the primary efficacy endpoints met within 12-16 weeks. Acitretin is a category B guideline recommendation as monotherapy for plaque psoriasis, with full treatment response expected within 3-6 months.

- Per the 2019 Joint AAD-NPF guidelines of care for the management and treatment of PsO with biologics: biologic agents, as monotherapy or combined with other topical or systemic medications, have a high benefit-to-risk ratio. Tumor necrosis factor inhibitors (TNFi) and inhibitors of IL-12/IL-23, IL-23, and IL-17 have a category "A" recommendation as a monotherapy treatment option for adult patients with moderate-to-severe plaque PsO. Guidelines do not recommend one product over another and note the similar efficacy seen across biologics within the same class. Use of products with the lowest net cost therefore provide the greatest value.
- The guidelines have not been updated to include Bimzelx. Additionally, there are no published, robust studies to support the use of more than one biologic product or targeted DMARD in combination.
- Psoriatic Arthritis
- PsA is a chronic inflammatory disease often associated with psoriasis. Psoriasis is an autoimmune disease affecting the skin, resulting in scaly red and white patches. These patches, called plaques, may appear anywhere on the body. The inflammation may also develop in the joints, which is classified as PsA. PsA occurs in up to 30% of patients with psoriasis, most commonly appearing between the ages of 30 and 50. PsA causes pain, stiffness, and swelling in and around the joints. If not properly treated, progressive joint damage may occur.
- Per the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guideline for the treatment of psoriatic arthritis:
- All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.
- In treatment-naïve patients, oral systemic medications (OSMs), such as methotrexate, sulfasalazine, cyclosporine, and leflunomide, may be used in patients without severe psoriatic arthritis and without severe psoriasis. OSMs have robust longitudinal safety and efficacy data in patients with PsA. Maximal response to OSMs are most commonly achieved within 3 months of therapy.
- If PsA remains active despite OSM therapy, switching to a tumor necrosis factor inhibitor (TNFi), an IL-17 inhibitor (IL-17i), or an IL-12/23i is recommended over switching to a different OSM; switching to a TNFi biologic over an IL-17i or IL-12/23i biologic is conditionally recommended in this scenario based on moderate quality evidence. Additional treatment options include Orencia (abatacept) and Xeljanz (tofacitinib). The detailed recommendations for subsequent therapies can be found in the 2018 ACR/NPF guideline for the treatment of psoriatic arthritis
- Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis
- Axial spondyloarthritis, comprising AS and NRAS, is the main form of chronic inflammatory arthritis affecting the axial skeleton. Non-radiographic means that damage to the joints is not visible on X-ray. When changes to the vertebrae (the bones of the spine)

or sacroiliac joints don't show any changes on an X-ray, that's known as NRAS. Once the joints are clearly affected on an X-ray, a person can be diagnosed with AS.

- The 2019 American College of Rheumatology recommendations for AS and NRAS are similar. In adult patients who have active disease despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDS), treatment with TNFi are recommended. They do not recommend any particular TNFi as the preferred choice for the typical patient. Cosentyx® (secukinumab) or Taltz (ixekizumab) is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi, whereas for patients with a secondary nonresponse (i.e. those who relapse after an initial response) it may be beneficial to switch to a different TNFi rather than immediately switch to a different biologic class. In the case of nonresponse (primary or secondary), the guidelines recommend against switching to treatment with a biosimilar since clinical response would not be expected to be different.
- Hidradenitis Suppurativa
- Hidradenitis suppurativa (HS) also known as acne inversa, is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions.
- Per the 2019 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:
- Systemic antibiotics have been a mainstay of HS treatment for decades, with many regimens reported. Tetracyclines are recommended in mild-to-moderate HS for a 12-week course or as long-term maintenance when appropriate. Clindamycin and rifampin in combination is effective as a second-line treatment for mild-to-moderate disease or as a first-line or adjunct treatment in severe disease. Moxifloxacin, metronidazole, and rifampin in combination are recommended as second- or third-line treatment in moderate-to-severe disease. Dapsone may be effective as maintenance therapy.
- For moderate to severe disease (i.e., inflammatory lesions with skin tunnels or scarring; Hurley stage II or III disease) that is unresponsive to at least one oral antibiotic, biologic therapy may be indicated. Adalimumab was the first systemic biologic FDA approved for moderate to severe HS and is recommended by the 2019 guidelines to improve disease severity and quality of life in patients with moderate to severe HS. The guidelines have not been updated to include other biologics approved for HS, including bimekizumab and secukinumab.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 02/12/2026	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 12/12/2024	Added criteria for the following new indications: psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, and hidradenitis suppurativa
1.1	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.0	Effective Date: 02/12/2024	New Policy

Botulinum Toxin Type A
Botox® (onabotulinumtoxinA) J0585
Daxxify® (daxibotulinumtoxinA) J0589
Dysport® (abobotulinumtoxinA) J0586
Xeomin® (incobotulinumtoxinA) J0588

Background Information:

- Botulinum toxin is a neurotoxin that is injected into a muscle to cause temporary paralysis of that muscle through the inhibition of acetylcholine release from peripheral cholinergic nerve endings. There are three commercial botulinum toxin type A products available: Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), and Xeomin (incobotulinumtoxinA). These agents differ in their manufacturing, isolation and purification processes and utilize different Clostridium batches.
- At comparable doses, the botulinum toxin A can be considered therapeutically equated. Data are limited and one botulinum toxin A product is not considered superior to the others. Botulinum toxin A products are not interchangeable and require medical expertise to convert patients from one formulation to another.
-

Appendix 1: International Headache Society Classification of Chronic Migraine Headache

A. Headache (tension-type or migraine) on 15 or more days per month for at least 3 months.*
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for a migraine without an aura
C. On 8 or more days per month for at least 3 months headache has fulfilled criteria for pain and associated symptoms of migraine without aura in either or both of criteria 1 or 2 below:
    1. At least two of the following criteria a), b), c) and d) below are met:
        a) Unilateral location
        b) Pulsating quality
        c) Moderate or severe pain intensity
        d) Aggravation by or causing avoidance of routine physical activity
    2. Treated and relived by triptan(s) or ergot before the expected development of the above symptoms.
D. No medication overuse and not attributed to another causative disorder

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Appendix 2: Medications for Abortive Migraine Treatment

Class	Common Examples
Triptans	Imitrex® (sumatriptan), Maxalt®, Zomig®, Amerge® (naratriptan), Axert®, Frova®, Relpax®

Analgesics	Aspirin, acetaminophen
Non-steroidal Anti-inflammatory Drugs	Motrin® (ibuprofen), Naprosyn® (naproxen), Relafen® (nabumetone), Voltaren® (diclofenac), Orudis® (ketoprofen), Clinoril® (sulindac), Toradol®(ketorolac)

Appendix 3: Medications for Prophylaxis of Migraines

Class	**Accepted Examples**
Anticonvulsants	Depakote® (divalproex), Depakene® (sodium valproate), Topamax® (topiramate), Tegretol® (carbamazepine)
ACE inhibitor or Angiotensin Receptor Blocker	Zestril® (lisinopril), Atacand® (candesartan)
Beta Blockers	Inderal® (propranolol), Lopressor® (metoprolol), Tenormin® (atenolol), Corgard® (nadolol), Blocadren® (timolol), Bystolic® (nebivolol), Visken®(pindolol)
Calcium Channel Blockers	Procardia® (nifedipine), Cardizem® (diltiazem), Calan® (verapamil)
Antidepressants	Elavil® (amitriptyline), Effexor® (venlafaxine)
CGRP inhibitors	Nurtec ODT (rimegepant), Qulipta (atogepant), Aimovig (erenumab), Ajovy (fremanezumab), Emgality (galcanezumab), Vyepti (eptinezumab)

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Policy History		
#	Date	Change Description
1.7	Effective Date: 10/09/2025	Updated criteria to specify that functional impairment has been “observed”
1.6	Effective Date: 04/10/2025	Updated incontinence to specify urinary incontinence and included treatment for complex and large or recurring ventral/abdominal hernia prior to abdominal wall reconstruction
1.5	Effective Date: 10/12/2023	Added Daxxify to policy
1.4	Effective Date: 08/10/2023	Annual Review
1.3	Effective Date: 08/04/2022	Updated Appendix 3 to include CGRP inhibitors
1.2	Effective Date: 12/09/2021	Removed prescriber requirements and rebound headache criteria for migraine to align with CGRP inhibitor criteria.
1.1	Effective Date: 04/08/2021	Updated criteria sections for: • Migraine headache: removed not to be used in combination with CGRP criteria • NDO: updated verbiage to state t/f two anticholinergics or other agents • OAB: Aligned criteria with Rx benefit by requiring t/f two agents for OAB Included expert opinion outreach regarding migraine combination therapy.
1.0	Effective Date: 01/01/2021	New Policy

Botulinum Toxin Type B Injection
Myobloc® (rimabotulinumtoxinB) J0587

Background Information:

- There are four botulinum neurotoxins marketed in the United States; 3 types A and 1 type B brands.
- Botulinum neurotoxins are produced by different biological manufacturing processes, obtained by different isolation and purification techniques and derived from different *Clostridium* batches.
- FDA labeling indicates that units of rimabotulinumtoxinB cannot be compared to or converted into units of any other botulinum toxin. Therefore, the efficacy, dosing and safety of rimabotulinumtoxinB cannot be based on extrapolation from other studies using other botulinum toxin serotypes.
- Use of botulinum toxin (all serotypes) for treatment of wrinkles or other cosmetic conditions is considered not medically necessary.
- Results from three clinical studies support the efficacy of rimabotulinumtoxinB in reducing neck pain and the severity of the abnormal head position associated with cervical dystonia or spasmodic torticollis in patients previously responsive to BTX-A or those patients who no longer respond to BTX-A.
    - Cervical dystonia (or spasmodic torticollis) is characterized by involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures.
- Anatomically guided injections of rimabotulinumtoxinB into the parotid and submandibular glands appear to effectively improve sialorrhea without causing dysphagia in patients with Parkinson's disease. A small trial in 20 subjects demonstrated a similar effect in patients with amyotrophic lateral sclerosis (ALS). A small trial in 26 subjects demonstrated a decrease in frequency and severity of sialorrhea in children with cerebral palsy who received a 3,000 MU injection of rimabotulinumtoxinB into the salivary glands.
- Use of botulinum toxic type B in other conditions
    - There are four pilot studies of 20 subjects each that investigate rimabotulinumtoxinB for use in palmer hyperhidrosis, axillary hyperhidrosis, refractory detrusor overactivity, and carpal tunnel syndrome. The evidence from these trials is of poor quality. Larger, well-designed trials are necessary to confirm the results.
    - Additional pilot studies, case reports and observational studies have suggested potential benefit of rimabotulinumtoxinB in the treatment of spasmodic dystonia, axillary hyperhidrosis, upper limb spasticity following stroke, spastic movement disorders in children and arm dystonia in children with cerebral palsy. The evidence from these trials is of poor quality. Larger, well-designed clinical trials are needed to assess safety and efficacy of rimabotulinumtoxinB in these conditions.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 12/04/2025	Annual review of criteria was performed, no changes were made
1.5	Effective Date: 12/12/2024	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 12/14/2023	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 12/01/2022	Updated to include trial and failure of preferred products statement
1.2	Effective Date: 10/06/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 10/07/2021	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 01/01/2021	New Policy

Breyanzi® (lisocabtagene maraleucel)
HCPCS: Q2054

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

- Breyanzi is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma. Breyanzi is also indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor; adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy; adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a BTK inhibitor; and adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least 2 prior lines of systemic therapy.

- Safety and efficacy as third-line therapy were established in the TRANSCEND trial, an open-label, multicenter, single-arm study of 268 patients with relapsed or refractory large B-cell Non-Hodgkin's lymphoma. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after at least 2 lines of systemic therapy or after allogeneic HSCT. For patients who received previous CD19-targeted therapy, CD19-positive lymphoma confirmed on a biopsy had to be confirmed since completing the prior CD19-targeted therapy. Patients were excluded from the study if they had an ECOG performance status of greater than 2, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, left ventricular ejection fraction (LVEF) less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, had active infection, or the presence of graft-vs-host disease. The primary endpoints were complete response (CR) rate and duration of response (DOR). Seventy-three percent of patients achieved a response (95% CI: 67% - 80%), including 54% who experienced CR (95% CI: 47% - 61%) and 19% who achieved a partial response (PR; 95% CI: 14% - 26%). Median duration of response was 16.7 months in all responders (95% CI: 5.3 – not reached (NR)). For patients who achieved a CR, median duration of response was not reached (95%

CI: 16.7 – NR). For patients achieving a PR, median duration of response was 1.4 months (95% CI: 1.1 – 2.2). Of 104 patients treated with Breyanzi who achieved a CR, 65% had remission lasting at least six months and 62% had remission lasting at least nine months.

- Safety and efficacy as second-line therapy were established in the TRANSFORM trial, a randomized, open-label, parallel-group, multicenter study of 184 patients with relapsed or refractory large B-cell Non-Hodgkin's lymphoma. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after first-line therapy. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 45 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. The primary endpoint was event free survival (EFS). Breyanzi significantly improved median EFS compared with standard therapy (10.1 months vs. 2.3 months; HR = 0.34; p-value < 0.0001) and also significantly increased median progression free survival (PFS) (14.8 months vs. 5.7 months; HR = 0.4; p-value = 0.0001). Sixty-six percent of patients assigned Breyanzi achieved complete response to therapy compared with 39% of patients assigned standard treatment (p-value < 0.0001).

- Safety and efficacy for use in CLL or SLL were established in the TRANSCEND-CLL 004, a phase 1/2, open-label, multicenter study of 65 patients with relapsed or refractory CLL or SLL who had received at least 2 prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. Of the evaluable patients, 45% and 20% achieved overall and complete responses, respectively. Of 13 MRD-evaluable patients, 100% and 92% achieved undetectable MRD in blood and marrow, respectively.

- Safety and efficacy for use in FL were established in the TRANSCEND-FL trial, a Phase II, open-label, multicenter, single-arm study of 94 patients with relapsed or refractory FL following at least 2 prior lines of therapy including an anti-CD20 monoclonal antibody and an alkylating agent. Patients must have had measurable disease. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. The primary endpoint was overall response rate (ORR). The ORR was 95.7% (95% CI: 89.5–98.8). The CR rate was 73.4% (95% CI: 63.3–82.0). The median DOR was not reached after a median follow-up of 16.8 months.

- Safety and efficacy for use in MCL were established in the TRANSCEND-MCL trial, a phase II, open-label, multicenter, single-arm study of 68 patients with relapsed or refractory MCL who had received at least two prior lines of therapy including a BTK inhibitor, an alkylating agent, and an anti-CD20 agent. Patients must have had measurable disease. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. The primary endpoint was ORR. The ORR was 85.3% (95% CI: 74.6, 92.7)

and 67.6% (95% CI: 55.2, 78.5) achieved a CR. The median DOR was 13.3 months (95% CI: 6.0, 23.3) with a median follow-up of 22.2 months (95% CI: 16.7, 22.8).

- Safety and efficacy for use in MZL were established in the TRANSCEND-MZL trial, a phase II, open-label, multicenter, single-arm study of 77 patients with relapsed or refractory MZL who had received at least two prior lines of therapy, including an anti-CD20 antibody and an alkylating agent, or who relapsed after hematopoietic stem cell transplant (HSCT). Patients must have had measurable disease. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, or had active infection. The primary endpoint was ORR. The ORR was 95.5% (95% CI: 87.3, 99.1) and 62.1% (95% CI: 49.3, 73.8) achieved a CR. The median DOR was not reached (95% CI: 25.59, NR).

- Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

- A provider portal platform is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.9	Effective Date: 02/12/2026	Updated to include the new indication for use in marginal zone lymphoma
1.8	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.7	Effective Date: 10/03/2024	Updated criteria under CLL and SLL indication to read no central nervous system involvement of the malignancy and no second malignancies in addition to CLL or SLL if the second malignancy has required therapy in the last 3 years or is not in complete remission

1.6	Effective Date: 06/06/2024	Updated to include new indications for use in relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), follicular lymphoma (FL), and mantle cell lymphoma (MCL)
1.5	Effective Date: 02/08/2024	Updated to add preliminary criteria for use in relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
1.4	Effective Date: 08/04/2022	Updated to align criteria across all CAR-T policies and include new indication for use as second-line therapy in DLBCL
1.3	Effective Date: 06/09/2022	Updated to add preliminary criteria for use as second-line therapy in DLBCL
1.2	Effective Date: 04/14/2022	Updated to remove CD19 requirement as NCCN guidelines state CAR-T can work without being positive for CD19 disease
1.1	Effective Date: 08/12/2021	New policy - this policy replaces previously approved criteria that was embedded in Chimeric Antigen Receptor-T Cell Class policy which will be retired
1.0	Effective Date: 01/01/2021	New policy

Calcitonin Gene Related Peptide (CGRP) Antagonists

Vyepti® (eptinezumab-jjmr) J3032

Background Information:

- Migraines affect 38 million people throughout the United States causing a significant decrease in quality of life and a large economic burden. An estimated 36 billion dollars are spent due to health care and loss of productivity costs. There is a large subset of migraine sufferers that are candidates for migraine prevention, but only a small portion of those candidates actually utilize these medications. Numerous drug classes have been studied for the prevention of migraine. The most recent guidelines published by the American Academy of Neurology in 2018 have shown efficacy for migraine prevention among antiepileptic drugs, antidepressants, antihypertensives, triptans (short term use for menstrually related migraines (MRM)), and botulinum toxin. In addition to drug therapy, neuromodulation and biobehavioral therapy have shown efficacy for the preventive and acute treatment of migraine.

- Guidelines suggest that there is no standard first line agent for the prevention of migraines; however, it does classify the agents by level of efficacy. Level A medications are those with established efficacy, Level B are probably effective, Level C are possibly effective, Level U are inadequate or conflicting data to support use, and Other are established as possibly or probably ineffective. There are many medications that are considered level A, as they have shown efficacy in >2 Class I trials. Divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, timolol, frovatriptan (short-term prophylaxis for treatment of MRM), and onabotulinumtoxinA are all Level A medications.

- Current abortive treatment options for migraines includes analgesics (such as NSAIDs), triptans and ergot alkaloids. Use of the latter is limited due to uncertainty of clear effectiveness and undesirable side effects. Reyvow® (lasmiditan), a first in class drug, was recently approved and is expected to be used in patients who are not candidates for triptans.

- Calcitonin gene related peptide (CGRP) antagonists are the first agents on the market that have a clearly understood mechanism of action in migraine prophylaxis. CGRP is the most potent endogenous vasodilator. Commonly, migraine sufferers present with elevated serum levels of CGRP even on non-migraine days. Inhibiting this pathway by binding to either the CGRP peptide itself or the CGRP receptor has proven to be an effective method in preventing migraine attacks in both episodic and chronic migraine.

- The American Headache Society publishes guidelines on all types of headache disorders including migraines. The most recent guidelines were published in 2018 and speak to the acute treatment and prophylaxis of migraines, both episodic and chronic. These guidelines incorporate CGRP antagonists for migraine therapy, which were absent from guidelines in previous years, as second line and adjunctive therapies for migraine prophylaxis in adults. The American Headache Society published guidelines for the treatment of cluster headache in 2016, however, these current guidelines do not include CGRP antagonists. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice from June 2021 continues to recommend adequate trials of established acute and/or preventive

treatments before initiating use of newer migraine-specific acute and preventive therapies, in part to due to cost considerations, and no published evidence supports or refutes this hierarchical approach

Appendix 1: Medications for Prophylaxis of Migraines

Class	Accepted Examples
Anticonvulsants	Depakote® (divalproex), Depakene® (sodium valproate), Topamax® (topiramate), Tegretol®
ACE inhibitor or Angiotensin Receptor Blocker	Zestril® (lisinopril), Atacand® (candesartan)
Beta Blockers	Inderal® (propranolol), Lopressor® (metoprolol), Tenormin® (atenolol), Corgard® (nadolol), Blocadren® (timolol), Bystolic® (nebivolol)
Calcium Channel Blockers	Procardia® (nifedipine), Cardizem® (diltiazem), Calan® (verapamil)
Antidepressants	Elavil® (amitriptyline), Effexor® (venlafaxine)
Botulinum Toxin	OnabotulinumtoxinA

Appendix 2: Pediatric Medications for Prophylaxis of Migraines[1]

Class	Accepted Examples
Anticonvulsants	Topamax® (topiramate), Depakote® (divalproex sodium), Depakene® (valproic acid)
Antihistamine	Periactin® (cyproheptadine)
Beta Blockers	Inderal® (propranolol),
Calcium Channel Blockers	Calan® (verapamil)
Antidepressants	Elavil® (amitriptyline)
Botulinum Toxin	OnabotulinumtoxinA

[1] Per the American Headache Society Preventive Therapy for Adolescents with Migraine – April 2021

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Policy History		
#	Date	Change Description
1.4	Effective Date: 10/09/2025	Updated criteria to reflect appropriate pediatric alternatives in Appendix 2 due to Ajovy's pediatric indication update.
1.3	Effective Date: 08/07/2025	Removed required HA day criteria
1.2	Effective Date: 04/10/2025	Annual review of criteria was performed, no changes were made
1.1	Effective Date:	Annual review of criteria was performed, no changes were made

	04/11/2024	
1.0	Effective Date: 09/01/2023	New Policy

Carvykti™ (ciltacabtagene autoleucel)
HCPCS: Q2056

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.
- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.
- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

    - Carvykti is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
    - Safety and efficacy for use as second-line therapy in relapsed or refractory multiple myeloma that is lenalidomide-refractory was established in the CARTITUDE-4 trial, an open-label, randomized, phase 3 study of 419 patients who received one to three prior lines of therapy, including a proteasome inhibitor (PI) and immunomodulatory agent (IMiD). The study excluded patients with a creatinine clearance of less than or equal to 40 mL/minute and an alanine aminotransferase greater than or equal to 3 times upper limit of normal. Patients were also excluded if absolute neutrophil count less than 1,000 cells/mm^3 and platelet count less than 75,000/mm^3. Patients were required to have measurable disease. The primary endpoint was progression free survival (PFS). At a median follow-up of 15.9 months, a 74% (HR = 0.26; 95% CI: 0.18, 0.38; p-value < 0.0001) reduction in the risk of disease progression or death was observed in patients randomized to the Carvykti arm compared to standard of care (SOC) treatments. Among patients in the Carvykti arm, median PFS was not reached and in the SOC arm, median PFS was 11.8 months. PFS at 12 months for patients in the Carvykti arm and SOC arm was 76% (95% CI: 69, 81) and 49% (95% CI: 42, 55), respectively. At the data cut-off, patients randomized to the Carvykti arm achieved an 85% overall response rate (ORR) and 73% achieved a complete response (CR) or better. Among patients in the SOC arm, the ORR was 67% and CR or better was 22%.
    - Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

- While use of Carvykti has not been established in patients with a creatinine clearance of less than 40 mL/minute, other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other CAR-T therapies support their use in these patients, Carvykti should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 ml/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.
- While use of Carvykti has not been established in patients with an alanine aminotransferase of greater than 3 times the upper limit of normal (ULN), other CAR-T therapies have been studied in subjects with an alanine aminotransferase of up to 5 times the ULN and the CTCAE recommendations have set 5 times the ULN as the cutoff for grade 2 adverse reactions. As the classification system uses 5 times the ULN and other CAR-T therapies have data supporting use in this patient population, Carvykti should be tolerated in these patients as well. As there is no data to support the administration of CAR-T at levels higher than 5 times the ULN, therapy should not be given to patients not meeting that threshold.
- The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. While Carvykti has only been studied in patients with a LVEF greater than or equal to 45%, there is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Carvykti should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.
- A provider portal that is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 06/05/2025	Annual review of criteria was performed; no changes were made
1.4	Effective Date: 06/06/2024	Updated to include the new indication for use as second-line therapy for relapsed or lenalidomide-refractory multiple myeloma
1.3	Effective Date: 02/08/2024	Updated to include preliminary criteria for use as second-line therapy for relapsed or lenalidomide-refractory multiple myeloma
1.2	Effective Date: 08/04/2022	Updated to align criteria across all CAR-T policies
1.1	Effective Date: 04/14/2022	New Policy
1.0	Effective Date: 03/07/2022	New Policy

Casgevy™ (exagamglogene autotemcel)
HCPCS: J3392

Background Information:

- Casgevy is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) and transfusion-dependent β-thalassemia (TDT).

- Sickle cell disease

    - Sickle cell disease is a recessive hemolytic anemia caused by a mutation in the β-globin gene. It is characterized by the formation of sickle hemoglobin (HbS). HbS is less soluble and less elastic than fetal hemoglobin (HbF) or normal adult hemoglobin (HbA). The disease involves multicellular adhesion between sickled red blood cells, white blood cells, platelets, and endothelial cells resulting in vaso-occlusive crises (VOCs). VOCs are the hallmark of SCD and are experienced by approximately 70% of patients. They are recurring, unpredictable, painful events that decrease organ function with complications including stroke, pneumonia, vision loss, pulmonary hypertension, leg ulcers, and sepsis. VOCs are often treated as an emergency requiring acute care and are the number one reason patients with SCD visit the emergency room or are hospitalized.

    - Hydroxyurea is a ribonucleotide reductase inhibitor which increases the amount of circulating HbF in the body and has been a mainstay of therapy. It also has been shown to lower the number of circulating leukocytes and reticulocytes altering the expression of adhesion molecules; raise red blood cell (RBC) volume; and improve cellular deformability and rheology, all of which contribute to a decrease in VOCs. The 2014 National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease Guidelines recommend the use of hydroxyurea for the following patient populations:

        - In adults with SCD who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period

        - In adults with SCD who have sickle cell-associated pain that interferes with daily activities and quality of life

        - In adults with SCD who have a history of severe and/or recurrent acute coronary syndrome

        - In adults with SCD who have severe symptomatic chronic anemia that interferes with daily activities or quality of life

        - In infants 9 months of age and older, children, and adolescents with SCD, offer treatment with hydroxyurea regardless of clinical severity to reduce complications

    - In adults and children with SCD who have chronic kidney disease and are taking erythropoietin

- The guidelines recommend starting hydroxyurea at a dose of 15 mg/kg/day for adults and increasing the dose by 5 mg/kg/day every 8 weeks to a maximum dose of 35 mg/kg/day. A clinical response to therapy may take 3 – 6 months. Therefore, a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. Guidelines have not yet been updated to include recommendations for use of gene therapy.

- Safety and efficacy for use in SCD were evaluated in the phase III CLIMB-121 trial, a single arm, multicenter study of 31 patients 18 to 35 years of age with severe SCD and documented βS/βS or βS/β0 genotype. Severe SCD was defined by the occurrence of at least 2 of the following events each year during the 2-year period before screening, while receiving appropriate supportive care (pain management plan, hydroxyurea if indicated): an acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions; acute chest syndrome (ACS), as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever; priapism lasting greater than 2 hours; and/or splenic sequestration. Participants could not have any of the following: positive presence of HIV-1 or HIV-2, hepatitis B, or hepatitis C; white blood cell count less than 3×10^9/L or platelet count less than 50×10^9/L not related to hypersplenism; advanced liver disease defined as alanine transferase greater than 3 times the upper limit of normal, total bilirubin greater than 2 times the upper limit of normal, baseline prothrombin time 1.5 times the upper limit of normal, or history of cirrhosis, any evidence of bridging fibrosis, or active hepatitis; prior treatment with an allogenic stem cell transplant; and prior or current malignancy or immunodeficiency disorder. The primary endpoint was the proportion of VOC-free responders, defined as patients who did not experience any protocol-defined severe VOCs for at least 12 consecutive months within the first 24 months after Casgevy infusion. The proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period was also assessed. The median (min, max) time to the last RBC transfusion was 19 (11, 52) days following Casgevy infusion. The proportion of VOC-free responders was 93.5% (29/31, 98% one-sided CI: 77.9%, 100.0%). The 29 VOC-free responders did not experience a protocol defined severe VOC during the evaluation period with a median duration of 22.2 months at the time of the interim analysis. One VOC-free responder, after initially achieving a response, experienced an acute pain episode meeting the definition of a severe VOC at month 22.8 requiring a 5-day hospitalization; this patient was reported to have a parvovirus B19 infection at the time. Of the 31 patients evaluable for VOC-free response, one patient was not evaluable for hospitalization-free response; the remaining 30 patients achieved the endpoint (100% [98% one-sided CI: 87.8%, 100.0%]).

- There is currently no data supporting administration of Casgevy following administration of another gene therapy. Casgevy should not be given following any other gene therapy for SCD as safety and efficacy has not been established.

- Transfusion Dependent β-thalassemia (TDT)

- The term “thalassemia” refers to a group of blood disorders characterized by a decrease or absence of synthesis of normal hemoglobin globulin chains. According to the chain whose synthesis is impaired, the thalassemias are call α-, β-, γ-, δ-, δβ-, or εγδβ-thalassemias. Beta-thalassemias result from a genetic defect in the HBB gene leading to a reduction in production of β-globulin chains, an excess of α-globulin chains, and a decrease in functioning hemoglobin. Low levels of hemoglobin cause a lack of oxygen in many parts of the body and anemia. People with anemia in beta-thalassemia often require lifelong blood transfusions for survival and subsequent treatment for iron overload due to these transfusions.

- The 2021 International Thalassemia Federation guidelines for transfusion dependent thalassemias recommend diagnosis should begin with genetic testing because of the extreme diversity in clinical severity of thalassemia subtypes. The degree of excess nonfunctional α-chains is the major predictor of disease severity. The less β-globulin production, the more non-functional α-chains in the bloodstream. β_0-thalassemia refers to the complete absence of production of β-globulin. When patients are homozygous for a β_0-thalassemia gene, they cannot make any normal β-chains. β_+-thalassemia indicates a mutation that presents decreased but not absent production of β-globulin. In thalassemia patients in which one or both of their β-thalassemia mutations are β_+-mutations, the disorder may be less severe. Beta-thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta-thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype. Casgevy is not being studied in patients with S/β-thalassemia or α-thalassemia. Patients with other β-thalassemia subtypes that were transfusion dependent are being included in the clinical trial.

- Treatment guidelines also recommend all patients undergo at least an annual comprehensive assessment at a thalassemia center. During such an assessment, recommendations are summarized after consultation with multiple specialists including a hematologist, a nurse specialist, a hepatologist, a cardiologist, an endocrinologist, a psychologist, a genetics counselor, a social worker, and a dietitian.

- Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. Continuation of infusions can be assessed by withholding transfusions and monitoring weekly hemoglobin levels. If the hemoglobin drops under 7 g/dL on two occasions two weeks apart, then regular transfusions should be commenced. Guidelines define a patient as transfusion dependent when they are getting infusions of packed red blood cells every 2 – 5 weeks to maintain the pre-transfusion hemoglobin of 9 g/dL - 10.5 g/dL and the post-transfusion hemoglobin less than 14 - 15 g/dL. This translates to approximately 100 mL/kg/year of packed red blood cells.

- Safety and efficacy were evaluated in the CLIMB-111 trial which included 44 patients with TDT. Participants could not have a prior hematopoietic stem cell transplant (HSCT) or currently be eligible for a HSCT with an HLA matched family donor, presence of HIV-1 or HIV-2 infection, a current immunodeficiency disorder or malignancy, or an uncorrected bleeding disorder. Patients also could not have advanced liver disease defined as alanine transferases or direct bilirubin greater than 3 times the upper limit of normal (ULN); or baseline prothrombin time or partial thromboplastin time greater than 1.5 times the ULN suspected of arising from liver disease; or magnetic resonance imaging (MRI) of the liver demonstrating clear evidence of cirrhosis. The primary endpoint was the proportion of participants achieving transfusion reduction for at least 6 months. Overall, 42 of 44 patients with TDT stopped red blood cell (RBC) transfusions. The

median time since last transfusion was 9.0 (0.8 - 36.2) months, with 16 patients having at least 12 months since their last transfusion. The two patients that had not yet stopped transfusions had 75% and 89% reductions in transfusion volume. By month 3, increases in HbF and mean total hemoglobin levels (> 9 g/dL) were achieved, with mean total hemoglobin levels increasing to and maintained at greater than 11 g/dL thereafter. At month 6, the mean proportion of edited alleles in bone marrow CD34+ hematopoietic stem and progenitor cells (HSPCs) and peripheral blood mononuclear cells was 74.3% and 63.4%, respectively which remained stable in all patients with greater than or equal to 1 year of follow-up.

- There is currently no data supporting administration of Casgevy following administration of another gene therapy. Casgevy should not be given following any other gene therapy for TDT as safety and efficacy has not been established.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 12/04/2025	Updated to allow use in patient who have used at least 10 units/year of packed red blood cells within the 2 years prior to Casgevy administration
1.4	P&T Date: 06/05/2025 Effective Date: 07/21/2025	Updated to include the required use of a provider portal to submit clinical outcomes data after Casgevy administration
1.3	Effective Date: 12/12/2024	Updated to allow use of electrophoresis for diagnosis of sickle cell disease and changed the authorization period from 6 months to 12 months
1.2	Effective Date: 04/11/2024	Updated to include the new FDA approved indication of transfusion-dependent β-thalassemia
1.1	Effective Date: 02/08/2024	New policy - replaces previously approved preliminary criteria
1.0	Effective Date: 01/02/2024	New policy

Cimzia® (certolizumab pegol)
HCPCS: J0717

Background Information:

- Cimzia is an anti-tumor necrosis factor (TNF) agent indicated for:
  - Adults with moderately to severely active rheumatoid arthritis
  - Adults with active psoriatic arthritis
  - Adults with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy
  - Adults with active ankylosing spondylitis
  - Adults with active non-radiographic axial spondyloarthritis
  - Adults with moderate-to-severe psoriasis who are candidates for systemic therapy or phototherapy
  - Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis

- Rheumatoid Arthritis (RA)

- The 2021 American College of Rheumatology (ACR) Guidelines for the Treatment of Rheumatoid Arthritis (RA) established recommendations for the care of adult RA patients. The guidelines state that treatment decisions should follow a shared decision-making process and should be reevaluated within a minimum of 3 months based on the efficacy and tolerability of the DMARD(s) chosen.

- For the initial treatment of symptomatic RA, the guidelines strongly recommend the use of conventional synthetic disease-modifying antirheumatic drug (csDMARD) monotherapy in those who are DMARD-naive. csDMARD monotherapy is a less costly first line treatment option with an extensive safety record accompanied by well-documented clinical efficacy and a large body of clinical experience and familiarity among prescribers. csDMARDs in the guidelines refer to methotrexate (MTX), hydroxychloroquine, leflunomide (LEF), and sulfasalazine. Azathioprine, cyclosporine, minocycline, and gold were not included due to their infrequent use in RA and lack of new data since the prior guidelines were published. Oral MTX is recommended as the preferred initial DMARD for patients with moderate-to-high disease activity, and hydroxychloroquine is recommended as the preferred initial DMARD for patients with low disease activity.

- If disease activity remains moderate or high despite optimal dosing of methotrexate monotherapy, the use of dual therapy with methotrexate plus biologic DMARD (bDMARD; etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, sarilumab, rituximab) or targeted synthetic DMARD (tsDMARD; tofacitinib, baricitinib, upadacitinib) therapy is conditionally recommended over the use of triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine). The guidelines do not inform preference of bDMARD over tsDMARD therapy (or vice-versa) for use in combination with MTX. No one agent has been shown to be superior to another. The guidelines do

acknowledge the emergence of safety signals for the JAK inhibitor class (tsDMARD), and state that further modification of this recommendation may be necessary as additional data are published.

– A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a pre-defined target (low disease activity or remission).

- Psoriatic Arthritis (PsA)

– Psoriatic Arthritis (PsA) is a chronic inflammatory disease often associated with psoriasis. Psoriasis is an autoimmune disease affecting the skin, resulting in scaly red and white patches. These patches, called plaques, may appear anywhere on the body. The inflammation may also develop in the joints, which is classified as PsA. PsA occurs in up to 30% of patients with psoriasis, most commonly appearing between the ages of 30 and 50. PsA causes pain, stiffness, and swelling in and around the joints. If not properly treated, progressive joint damage may occur.

– Per the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guideline for the treatment of psoriatic arthritis:

– All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.

– In treatment-naïve patients, oral systemic medications (OSMs), such as methotrexate, sulfasalazine, cyclosporine, and leflunomide, may be used in patients without severe psoriatic arthritis and without severe psoriasis. OSMs have robust longitudinal safety and efficacy data in patients with PsA. Maximal response to OSMs are most commonly achieved within 3 months of therapy.

– If PsA remains active despite OSM therapy, switching to a TNFi, an interleukin 17 inhibitor (IL-17i), or an interleukin 12/23 inhibitor (IL-12/23i) is recommended over switching to a different OSM; switching to a TNFi biologic over an IL-17i or IL-12/23i biologic is conditionally recommended in this scenario based on moderate quality evidence. Additional treatment options include Orencia® (abatacept) and Xeljanz® (tofacitinib). The detailed recommendations for subsequent therapies can be found in the 2018 ACR/NPF guideline for the treatment of psoriatic arthritis.

- Ankylosing Spondylitis (AS)

– Axial spondyloarthritis, comprising ankylosing apondylitis (AS) and non-radiographic axial spondyloarthritis (NRAS), is the main form of chronic inflammatory arthritis affecting the axial skeleton. Non-radiographic means that damage to the joints is not visible on X-ray. When changes to the vertebrae (the bones of the spine) or sacroiliac joints don’t show any changes on an X-ray, that’s known as NRAS. Once the joints are clearly affected on an X-ray, a person can be diagnosed with AS.

- The 2019 American College of Rheumatology recommendations for AS and NRAS are similar. In adult patients who have active disease despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDS), treatment with TNFi are recommended. They do not recommend any particular TNFi as the preferred choice for the typical patient. Cosentyx® (secukinumab) or Taltz® (ixekizumab) is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi, whereas for patients with a secondary nonresponse (i.e. those who relapse after an initial response) it may be beneficial to switch to a different TNFi rather than immediately switch to a different biologic class. In the case of nonresponse (primary or secondary), the guidelines recommend against switching to treatment with a biosimilar since clinical response would not be expected to be different.

- Crohn's disease (CD)

- The 2018 American College of Gastroenterology (ACG) guidelines establish therapeutic recommendations for patients with Crohn's disease based upon disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Current therapeutic approaches should be considered a sequential continuum to treat acute disease or induce clinical remission and then to maintain response/remission. In general, clinical evidence of improvement should be evident within 2 – 4 weeks and the maximal improvement should occur within 12 – 16 weeks. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease, have their medication dose adjusted in order to attempt to optimize therapy, or advance to treatment for moderate to severe disease according to their clinical status.

- Corticosteroids are used primarily for the treatment of flares of CD. Conventional corticosteroids are effective for reducing the signs and symptoms of active CD and induction of remission in patients with moderately to severely active CD. Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active disease. The ACG guidelines recommend prednisone equivalent doses ranging from 40 to 60 mg per day. These doses are typically maintained for 1 –2 weeks and tapered at 5 mg weekly until 20 mg and then 2.5 –5 mg weekly. Once begun, care should be taken to ensure that corticosteroids are successfully discontinued, and steroid-sparing agents should be used.

- In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, mercaptopurine, azathioprine, and intramuscular or subcutaneous methotrexate are effective as steroid-sparing agents and are recommended by the guidelines. Maximum effectiveness of these agents can be seen between 8 to 12 weeks from therapy initiation. Methotrexate is also recommended in combination with steroids as effective for treatment of moderately active steroid-dependent/resistant CD. Cyclosporine, tacrolimus, and mycophenolate are not recommended for treatment of CD.

- Biologics, such as TNFi are recommended to treat CD that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. The ACG guidelines also recommend the use of biologics in combination with immunosuppressants to help decrease the formation of antibodies against the biologic therapy. There are no robust, published studies to support use of biologic agents in combination.

- The 2021 American Gastroenterological Association (AGA) guidelines include similar recommendations for the management of moderate-to-severe CD compared to the recommendations cited in the 2018 ACG guidelines. Both guidelines recommend corticosteroids over no treatment for induction of remission. Additionally, both guidelines recommend thiopurines, such as azathioprine or 6-mercaptopurine, as steroid-sparing agents for maintenance of remission. The AGA guidelines also recommend the same biologic agents cited in the ACG guidelines for treatment of CD, with the exception of Tysabri® (natalizumab), which the AGA suggests against use of due to its associated risk of progressive multifocal leukoencephalopathy (PML).

- Of note, the AGA guidelines conditionally recommend earlier introduction of biologic therapy prior to failure of corticosteroids; however, this recommendation is supported by a low level of clincial evidence. To date, no blinded randomized controlled trials (RCTs) have demonstrated the superiority of early introduction of biologic therapy compared to conventional induction therapy with corticosteroids followed by steroid-sparing therapy. The 2021 AGA guideline authors also acknowledge that earlier therapy with either combination immunomodulotor plus biologic therapy or biologic monotherapy may result in over-treating some patients and potentially exposing them to treatment-related risks and costs with limited benefit.

- Psoriasis (PsO)

- Psoriasis is a chronic, painful and life-altering immune-mediated disease which predominantly manifests with skin and joint involvement. Patients may also experience significant cardiovascular and psychological comorbidities. Approximately 2% of U.S. adults are affected by psoriasis (men and women equally), and it can occur at any age. Approximately 90% of psoriasis-affected patients have plaque psoriasis, which is characterized by well-defined round or oval plaques that vary in size and often coalesce. The severity of psoriasis is defined as: mild = less than 3% of body affected; moderate = 3-10% of body affected; and severe being more than 10% of the body affected.

- Per the 2020 Joint American Academy of Dermatology - National Psoriasis Foundation (AAD-NPF) guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures: topical corticosteroids provide a high efficacy and good safety option for patients with localized disease. They are generally recommended as first-line therapy. Choice of steroid potency may depend on severity, location, patient preference, and patient age, while the duration of treatment may vary with steroid potency, location and severity of disease often ranging from 2-12 weeks. Therapeutic regimens may include 2-4 weeks with a topical steroid applied twice daily, followed by a maintenance regimen where topical steroids are alternated with a steroid-sparing topical agent. Treatment with topical steroids for over 12 weeks is recommended under careful supervision by a physician.

- Per the 2019 AAD-NPF guidelines of care for the management and treatment of psoriasis with phototherapy: phototherapy serves as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications or simply seeking an adjunct to a failing regimen. Guidelines also state that the majority of patients with mild-to-moderate disease have adequate disease control with topical therapies and phototherapy alone.

- Per the 2020 Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with systemic nonbiologic therapies: many oral medications, including methotrexate, cyclosporine, and acitretin, have been used for decades to treat psoriasis, each with its own benefits and risks. Most work by targeting the immune system, whereas others, such as acitretin, work predominantly by decreasing keratinocyte hyperproliferation, thus restoring the normal epidermal differentiation. Both methotrexate and cyclosporine are category A guideline recommendations for the treatment of moderate to severe psoriasis in adults and for severe, recalcitrant psoriasis, respectively. Studies examining the use of methotrexate and cyclosporine in psoriasis showed the primary efficacy endpoints met within 12-16 weeks. Acitretin is a category B guideline recommendation as monotherapy for plaque psoriasis, with full treatment response expected within 3-6 months.

- Per the 2019 Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics: biologic agents, as monotherapy or combined with other topical or systemic medications, have a high benefit-to-risk ration. TNFi and IL-12/IL-23i, IL-23i, and IL-17i biologics have a category "A" recommendation as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis. Guidelines do not recommend one product over another and note the similar efficacy seen across biologics within the same class. There are no published, robust studies to support the use of more than one biologic product in combination.

- Non-Radiographic Axial Spondyloarthritis (NRAS)

- Axial spondyloarthritis, comprising ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (NRAS), is the main form of chronic inflammatory arthritis affecting the axial skeleton. Non-radiographic means that damage to the joints is not visible on X-ray. When changes to the vertebrae (the bones of the spine) or sacroiliac joints don’t show any changes on an X-ray, that’s known as NRAS. Once the joints are clearly affected on an X-ray, a person can be diagnosed with AS.

- The 2019 American College of Rheumatology recommendations for AS and NRAS are similar. In adult patients who have active disease despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDS), treatment with TNFi are recommended. They do not recommend any particular TNFi as the preferred choice for the typical patient. Cosentyx (secukinumab) or Taltz is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi, whereas for patients with a secondary nonresponse (i.e. those who relapse after an initial response) it may be beneficial to switch to a different TNFi rather than immediately switch to a different biologic class. In the case of nonresponse (primary or secondary), the guidelines recommend against switching to treatment with a biosimilar since clinical response would not be expected to be different.

- Polyarticular Juvenile Idiopathic Arthritis (pJIA)

- Juvenile idiopathic arthritis (JIA) defines a collection of inflammatory arthritides of unknown etiology. JIA onset is prior to 16 years of age with a minimum duration of 6 weeks and other potential causes of synovitis are excluded. JIA can be subdivided into pJIA and systemic JIA.

- pJIA is defined by the presence of more than 4 affected joints in the first 6 months of illness and comprises 20-30% of children with JIA. Therapy is directed toward treating the underlying inflammation and preventing JIA-associated complications and adverse effects of its treatment.

- The 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF) guideline for the treatment of JIA strongly recommends initial therapy for pJIA with a DMARD such as MTX or LEF. MTX is conditionally recommended over LEF as it has a greater volume of data supporting its effectiveness compared to LEF and can be administered subcutaneously (recommended) or orally. The guidelines consider an adequate trial of a DMARD to be 3 months.

- If moderate or high disease activity persists despite adequate DMARD use, the ACR/AF guidelines recommend biologic agents either in combination with a DMARD or as monotherapy in certain situations. Biologic agents FDA approved for pJIA in patients 2 years of age and older include Humira® (adalimumab), Enbrel® (etanercept), tocilizumab, Orencia® (abatacept), Simponi Aria® (golimumab), Xeljanz® (tofacitinib), Xeljanz (tofacitinib) oral solution, and Cimzia (certolizumab pegol).

- Of note, biologic therapy may be an appropriate initial therapy in pJIA patients with risk factors and involvement of high-risk joints, high disease activity, and/or for those judged to be at high risk of disabling joint damage.

- There is the most experience with tumor necrosis factor inhibitors (TNFi; Humira, Enbrel, Simponi Aria) as initial biologic therapy; however, the preferred class of initial biologic is not specified in the guideline recommendations due to a lack of comparative data and the consideration that non-TNFi biologics may be preferred in certain patient-specific scenarios. If a TNFi is started as the initial biologic, switching to a non-TNFi (tocilizumab or Orencia) is recommended over switching to a second TNFi. An exception to this is for those who had a good initial response to the first TNFi.

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Policy History		
#	Date	Change Description
1.6	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Added criteria requiring member to self-administer unless clinically unable to do so
1.5	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.4	Effective Date: 12/14/2023	Annual review of criteria was performed, no changes were made

1.3	Effective Date: 12/01/2022	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 12/09/2021	Updated to remove FDA approved indications, the phototherapy and oral DMARD criteria for psoriasis, the oral DMARD criteria for psoriatic arthritis, and added criteria requiring trial of one topical corticosteroid for psoriasis
1.1	Effective Date: 02/04/2021	Removal of the topical steroid criteria for psoriasis indication
1.0	Effective Date: 01/01/2021	New Policy

Cinqair® (reslizumab)
HCPCS: J2786

Background Information:

- Cinqair is an interleukin-5 (IL5) antagonist monoclonal antibody (IgG4, kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

- Eosinophilic asthma is a sub phenotype of severe asthma characterized by elevated sputum and blood eosinophil levels as well as increased asthma severity, atopy, late-onset disease, and steroid refractoriness.

- Severe asthma requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite therapy. Add-on treatment for severe asthma includes LAMA, leukotriene receptor antagonist (LTRA), low dose azithromycin (adults) and biologic agents for severe allergic or severe type 2 asthma. Type 2 inflammation is found in majority of the of people with severe asthma and characterized by production of cytokines such as interleukin. Anti-IL5 monoclonal antibodies (Cinqair, Nucala, and Fasenra) specifically target the formation of eosinophils and deplete blood eosinophil levels.

- Add-on treatments for severe asthma include LAMAs, LTRA, low dose azithromycin (adults), and biologic agents for severe allergic or severe type 2 asthma. Type 2 inflammation is found in a majority of people with severe asthma and is characterized by the production of cytokines such as interleukin (IL). The Global Institute for Asthma (GINA) 2022 guidelines have the following recommendations for add-on biologic therapy for severe asthma:

  - Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4–5 treatment (Evidence A).

  - Add-on anti-interleukin-5/5R treatment (subcutaneous mepolizumab for patients aged ≥6 years; intravenous reslizumab for ages ≥18 years or subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4–5 treatment. Efficacy data for mepolizumab in children 6–11 years are limited to one very small open label uncontrolled study.

  - Add-on anti-interleukin-4Rα treatment (subcutaneous dupilumab) for patients aged ≥6 years with severe eosinophilic/Type 2 asthma, or for adults or adolescents requiring treatment with maintenance oral corticosteroids.

  - Add-on anti-thymic stromal lymphopoietin (anti-TSLP) (subcutaneous tezepelumab): for patients aged ≥12 years with severe asthma (Evidence A).

- Per the GINA 2023 guidelines, a trial of at least 4 months of an add-on biologic therapy is recommended before assessing response.

- A peripheral blood eosinophil count is an indirect way to estimate airway inflammation. A blood eosinophil count ≥ 300 cells/microliter may help to predict asthmatics who are at increased risk for exacerbations in the next year. Furthermore, a count-response relation exists between blood eosinophil counts and asthma-related outcomes. The European Respiratory Society/American Thoracic Society guidelines from 2020 suggest that treatment of severe asthma be guided by clinical criteria and biomarkers such as blood eosinophil levels or fractional exhaled nitric oxide (FeNO), rather than by clinical criteria alone. In addition, it also suggests that a blood eosinophil count cut-off point of ≥ 150 cells/microliter can be used to guide anti-IL5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations.

- Efficacy of Cinqair was evaluated versus placebo in four randomized, double-blind placebo-controlled trials of up to 52 weeks in a total of 981 patients.

- In Studies I and II, the primary endpoint was the frequency of clinically significant exacerbations of asthma. Patients receiving Cinqair 3 mg/kg once every 4 weeks experienced significantly fewer exacerbations in comparison to patients receiving placebo.

- Exacerbations requiring the use of a systemic corticosteroid as well as exacerbations resulting in hospitalization or an emergency room visit were each reduced with Cinqair 3 mg/kg.

- In Studies III and IV, the primary endpoint was forced expiratory volume in one second (FEV1). Patients receiving Cinqair showed a significant improvement in lung function through changes in FEV1.

- Review response to biologic therapy after 3-4 months of treatment. If the patient had a good response, the need for each medication should re-evaluated, but do not completely stop inhaled therapy. Consider gradually decreasing or stopping oral steroids first.

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Table 1: Comparative cumulative daily dosing of inhaled corticosteroids (mcg/day)

Inhaled Corticosteroid	Ages 12 and Up			Ages 6-11		
	Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
Beclometasone dipropionate HFA	100 – 200	>200 – 400	>400	50 – 100	>100 – 200	>200
Budesonide DPI	200 – 400	>400 – 800	>800	100 – 200	>200 – 400	>400
Budesonide nebules	NA	NA	NA	250 – 500	>500 – 1,000	>1,000
Ciclesonide HFA	80 – 160	>160 – 320	>320	80	>80 – 160	>160
Fluticasone furoate DPI	100	NA	200	NA	NA	NA
Fluticasone propionate DPI	100 – 250	>250 – 500	>500	100 – 200	>200 – 400	>400
Fluticasone propionate HFA	100 – 250	>250 – 500	>500	100 – 200	>200 – 500	>500
Mometasone furoate	110 – 220	>220 – 440	>440	110	≥220 - <440	≥440
Triamcinolone acetonide	400 – 1,000	>1,000 – 2,000	>2,000	400 – 800	>800 – 1,200	>1,200

Policy History		
#	Date	Change Description
1.7	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made.

1.6	Effective Date: 10/03/2024	Changed the “Cannot be used in combination with other biologics for asthma” criteria to “Not to be used in combination with other biologics or targeted DMARDs for the same indication”
1.5	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 04/06/2023	Updated to require a 4 month trial of guideline supported pharmacy benefit alternatives
1.3	Effective Date: 10/06/2022	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/07/2021	Updated LABA and LAMA requirement to LABA or LAMA
1.1	Effective Date: 06/10/2021	Criteria document created and criteria aligned between all biologic asthma agents. The criteria for asthma was previously part of the Biologics for Asthma Policy which will be retired after this P&T.
1.0	Effective Date: 01/01/2021	New Policy

Colony Stimulating Factors (CSFs)

Armlupeg™ (pegfilgrastim-unne) J3590
Filkri® (filgrastim-laha) J3590
Fulphila™ (pegfilgrastim-jmbd) Q5108
Fylnetra® (pegfilgrastim-pbbk) Q5130
Granix® (tbo-filgrastim) J1447
Leukine® (sargramostim) J2820
Neulasta® (pegfilgrastim) J2506
Neulasta On-Pro® (pegfilgrastim) J2506
Neupogen® (filgrastim) J1442
Nivestym™ (filgrastim-aafi) Q5110
Nypozi™ (filgrastim-txid) Q5148
Nyvepria™ (pegfilgrastim-apgf) Q5122
Releuko™ (filgrastim-ayow) Q5125
Rolvedon™ (eflapegrastim-xnsxt) J1449
Ryzneuta® (efbemalenograstim alfa-vuxw) J9361
Stimufend® (pegfilgrastim-fpgk) Q5127
Udenyca™ (pegfilgrastim-cbqv) Q5111
Udenyca Onbody™ (pegfilgrastim-cbqv) Q5111
Zarxio® (filgrastim-sndz) Q5101
Ziextenzo™ (pegfilgrastim-bmez) Q5120

Background Information:

- There are different types of colony stimulating factors (CSFs). Filgrastim-products, pegfilgrastim products and Leukine is the only sargramostim product. Filgrastim and pegfilgrastim products are human granulocyte colony-stimulating factors (G-CSFs). Leukine is a human granulocyte-macrophage CSF (GM-CSF).

- Filgrastim products:

    - Granix is FDA approved to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer medications associated with a clinically-significant incidence of febrile neutropenia. It is not technically considered a biosimilar because it was filed as a Biologics License Application since a biosimilars approval pathway had not been established at the time of FDA submission.

- Neupogen is approved 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 and fever.

    - Reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of adults with AML.

    - 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 BMT.

    - Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

    - Chronic administration to reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

    - Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).

    - All of Neupogen's biosimilars are approved for the same indications as Neupogen with the exception of use to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome) which Nivestym is not indicated for.

- Pegfilgrastim products:

    - Neulasta is approved 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. Limitation of Use: This agent is not indicated for mobilization of peripheral blood progenitor cells for HSCT.

        - Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome).

    - All of Neulasta' s biosimilars are approved for the same indications as Neulasta with the exception of increasing survival in patients acutely exposed to myelosuppressive doses of radiation. Armlupeg, Stimufend, Udenyca, and Ziextenzo are approved for this indication.

- Sargramostim is approved:

    - 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 of age with AML.

    - 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.

    - To accelerate myeloid reconstitution following autologous peripheral blood progenitor cell or bone marrow transplantation in adult and pediatric patients ≥ 2 years of age with non-Hodgkin's lymphoma, lymphoblastic leukemia, and Hodgkin's lymphoma.

    - For acceleration of myeloid reconstitution in adult and pediatric patients ≥ 2 years of age undergoing allogeneic bone marrow transplantation from HLA-matched related donors.

    - Treatment of adult and pediatric patients ≥ 2 years of age who have undergone allogeneic or autologous BMT in whom neutrophil recovery is delayed or failed.

    - 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).

- Eflapegrastim and efbemalenograstim alfa-vuxw are approved:

    - To decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia

- CSF products have an established role in the management of patients with non-myeloid malignancies who are receiving myelosuppressive anti-cancer agents, as well as for several other uses. Many studies have shown that the prophylactic use of these products reduces the incidence,

duration, and severity of febrile neutropenia, decrease the subsequent rates of infection and hospitalization, and improves the delivery of full-dose intensity chemotherapy on schedule in patients with various cancers.

- The National Comprehensive Cancer Network (NCCN) guidelines for various cancer and myeloid growth factors provides recommendations on the use of these agents. The criteria reflects these recommendations along with expert opinion.

- Regarding biosimilars, the NCCN guidelines state an FDA approved biosimilar is an appropriate substitution for its reference products.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 08/07/2025	Annual review performed - no changes to criteria
1.3	Effective Date: 08/08/2024	Updated to include Nypozi and add the statement that biosimilars will be approved for all indications of the innovator product when criteria is met
1.2	Effective Date: 04/11/2024	Updated to remove the chemotherapy intent requirement and include criteria for use in low risk febrile neutropenia
1.1	Effective Date: 02/08/2024	Updated to include Ryzneuta and Udenyca Onbody
1.0	Effective Date: 06/01/2023	New Policy

Cosentyx® IV (secukinumab)
HCPCS: C9166

Background Information:

- Cosentyx IV is an interleukin-17 (IL-17) receptor A antagonist indicated for the following:
    - Active psoriatic arthritis in patients 2 years of age and older
    - Adults with active ankylosing spondylitis
    - Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation

- Cosentyx is available in a self-administered subcutaneous (SC) formulation and an intravenous (IV) infusion for adults with psoriatic arthritis, active ankylosing spondylitis, and active NRAS. The IV formulation requires a healthcare provider for administration.
- Clinical reasons a patient may be unable to self-administer Cosentyx include:
    - Patient or caregivers are unable to perform subcutaneous injections with proper technique.
    - Member requires monthly medical support from the physician.

    - Psoriatic Arthritis
        - PsA is a chronic inflammatory disease often associated with psoriasis. Psoriasis is an autoimmune disease affecting the skin, resulting in scaly red and white patches. These patches, called plaques, may appear anywhere on the body. The inflammation may also develop in the joints, which is classified as PsA. PsA occurs in up to 30% of patients with psoriasis, most commonly appearing between the ages of 30 and 50. PsA causes pain, stiffness, and swelling in and around the joints. If not properly treated, progressive joint damage may occur.

        - Per the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guideline for the treatment of psoriatic arthritis:

            - All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.

            - In treatment-naïve patients, oral systemic medications (OSMs), such as methotrexate, sulfasalazine, cyclosporine, and leflunomide, may be used in patients without severe psoriatic arthritis and without severe psoriasis. OSMs have robust longitudinal safety and efficacy data in patients with PsA. Maximal response to OSMs are most commonly achieved within 3 months of therapy.

- If PsA remains active despite OSM therapy, switching to a tumor necrosis factor inhibitor (TNFi), an IL (interleukin)-17 inhibitor (IL-17i), or an IL-12/23i biologic is recommended over switching to a different OSM; switching to a TNFi biologic over an IL-17i or IL-12/23i biologic is conditionally recommended in this scenario based on moderate quality evidence. Additional treatment options include Orencia® (abatacept) and Xeljanz® (tofacitinib). The detailed recommendations for subsequent therapies can be found in the 2018 ACR/NPF guideline for the treatment of psoriatic arthritis.

- Ankylosing Spondylitis
  - Axial spondyloarthritis, comprising AS and NRAS, is the main form of chronic inflammatory arthritis affecting the axial skeleton. Non-radiographic means that damage to the joints is not visible on X-ray. When changes to the vertebrae (the bones of the spine) or sacroiliac joints don't show any changes on an X-ray, that's known as NRAS. Once the joints are clearly affected on an X-ray, a person can be diagnosed with AS.
  - The 2019 American College of Rheumatology recommendations for AS and NRAS are similar. In adult patients who have active disease despite treatment with NSAIDS, treatment with TNFi biologics are recommended. They do not recommend any particular TNFi as the preferred choice for the typical patient. Cosentyx® (secukinumab) or Taltz® (ixekizumab) is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi, whereas for patients with a secondary nonresponse (i.e. those who relapse after an initial response) it may be beneficial to switch to a different TNFi rather than immediately switch to a different biologic class. In the case of nonresponse (primary or secondary), the guidelines recommend against switching to treatment with a biosimilar since clinical response would not be expected to be different.

- Non-Radiographic Axial Spondyloarthritis
  - Axial spondyloarthritis, comprising AS and NRAS, is the main form of chronic inflammatory arthritis affecting the axial skeleton. Non-radiographic means that damage to the joints is not visible on X-ray. When changes to the vertebrae (the bones of the spine) or sacroiliac joints don't show any changes on an X-ray, that's known as NRAS. Once the joints are clearly affected on an X-ray, a person can be diagnosed with AS.
  - The 2019 ACR recommendations for AS and NRAS are similar. In adult patients who have active disease despite treatment with NSAIDS, treatment with TNFi are recommended. They do not recommend any particular TNFi as the preferred choice for the typical patient. Cosentyx (secukinumab) or Taltz (ixekizumab) is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi, whereas for patients with a secondary nonresponse (i.e. those who relapse after an initial response) it may be beneficial to switch to a different TNFi rather than immediately switch to a different biologic class. In the case of nonresponse (primary or secondary), the guidelines recommend against switching to treatment with a biosimilar since clinical response would not be expected to be different.

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Policy History		
#	Date	Change Description
1.2	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Added criteria requiring member to self-administer unless clinically unable to do so
1.1	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.0	Effective Date: 02/12/2024	New policy

Crysvita® (burosumab-twza)
HCPCS: J0584

Background Information:

- Crysvita is a FGF23 blocking antibody indicated for the treatment of XLH in adult and pediatric patients 6 months of age and older and the treatment of FGF23-related hypophosphatemia in TIO associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older.

- XLH is a hereditary phosphate wasting condition, caused by inactivating mutations in the phosphate-regulating endopeptidase homolog X-linked (PHEX) gene. This leads to an increase in FGF23 levels, which then causes renal wasting and decreased intestinal absorption of phosphate.

    - The diagnosis is confirmed with genetic testing for the PHEX mutation. However, genetic testing is not always necessary. For example, a patient with a family history consistent with the disease and biochemical features such as elevated FGF23 levels, low serum phosphate levels, and sign and symptoms consistent with the disease is sufficient to confirm the diagnosis and initiate treatment.

    - Skeletal abnormalities, including rickets, osteomalacia, and growth failure, are the major clinical findings in children with XLH. Although adults with XLH may have less obvious symptoms, they often have significant functional impairment and multiple complications, emphasizing that the disorder is truly lifelong and not simply a disorder of the growth plate that resolves with the cessation of growth.

- TIO is a rare, acquired paraneoplastic syndrome caused by tumoral overproduction of FGF23, which then causes renal wasting and decreased intestinal absorption of phosphate that acts primarily at the proximal renal tubule to inhibit phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D, which leads to hypophosphatemia and eventually osteomalacia.

    - Definitive treatment for TIO is complete tumor resection, which leads to prompt reversal of the biochemical abnormalities and healing of the bone disease over a period of 6 to 12 weeks.

    - However, the tumors that cause this syndrome are difficult to identify because they are small, slow growing, and may be found in bone or soft tissue anywhere in the body.

    - A diagnosis can be confirmed based on a combination of biochemical markers and history of clinical manifestations.

        - Biochemical markers which are consistent with the patient population from the clinical trial include:

        - Elevated serum FGF23 level. The reference range can range based on the laboratory used. The majority of patients with tumor induced osteomalacia have FGF23 levels above 2 times the upper limit of the reference interval.

        - Low serum phosphorus level.

        - Low ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR). TmP/GFR provides the most accurate assessment of renal phosphate handling to confirm renal tubular phosphate wasting.

    - Signs and symptoms include bone pain, muscle pain, and fatigue.

    - Treatment of choice is resection of the tumor and is almost always curative and provides rapid improvement

- The safety and efficacy of Crysvita was established based on clinical trials in patients with these conditions despite treatment with activated vitamin D and phosphate supplements. The standard of care when medical management is warranted, prior to the approval of Crysvita, was treatment with activated vitamin D and phosphate supplements as outlined in several published guidances.

- The Endocrine Society has released updated guidelines on XLH Management in Children (February 2025) and in Adults (April 2025). In the management of children, Endocrine Society recommends Crysvita therapy over conventional therapy (active vitamin and phosphate salts) strong recommendation. This recommendation also aligns with clinical practice recommendations for the diagnosis and management of XLH endorsed by multiple European Societies for Nephrology and Endocrinology (Janurary 2025) which recommends treating children and adolsecents (aged 1-17 years) with XLH and signs and/or radiological evidence of rickets with Crysvita as soon as the diagnosis is established (moderate recommendation). The approach to adults with XLH differs slightly than that of children. To date, no studies have directly compared the efficacy of Crysvita with that of oral phosphate supplements and active vitamin D for the treatment of XLH in adults. The Endocrine Society guidelines suggest treatment with Crysvita over conventional therapy but that is a conditional recommendation with low certainty. The European clinical practice recommendations only recommend treating adult patients with significant symptoms and manifesations of XLH. These clinical practice guidelines recommend beginning with active vitamin D together with oral phosphorus except in patients who have pseudofractures where Crysvita is preferred (grade C, weak recommendation).

- In 2021, the Endocrine Society published guidelines for the diagnosis and management of TIO. These guidelines recommend surgical resection of the tumor as first-line therapy for patients with TIO in whom the tumor can be identified and is considered operable as the removal of the tumor is usually curative and prevents tumor recurrence. If the lesion cannot be identified or is not resectable, the Endocrine Society recommends that either conventional therapy or Crysvita should be considered.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 12/04/2025	Updated criteria to remove active vitamin D and phosphate supplement step from pediatric patients with XLH. Updated formatting of steps to clarify listed requirements.
1.5	Effective Date: 12/12/2024	Annual review was completed, no changes to criteria
1.4	Effective Date: 12/14/2023	Annual review was completed, no changes to criteria
1.3	Effective Date: 12/01/2022	Annual review was completed, no changes to criteria
1.2	Effective Date: 12/09/2021	Removed physician requirement and the criteria requiring a score of 4 or greater on BPI question 3 for confirmation of XLH diagnosis.
1.1	Effective Date: 08/12/2021	Annual review was completed, no changes to criteria
1.0	Effective Date: 01/01/2021	New Policy

Denosumab Products

Aukelso™ (denosumab-kyqq) J3590
Bildyos® (denosumab nxxp) J3590
Bilprevda® (denosumab-nxxp) J3590
Bomyntra® (denosumab-bnht) Q5158
Bosaya™ (denosumab-kyqq) J3590
Boncresa™ (denosumab-mobz) J3590
Conexxence® (denosumab-bnht) Q5158
Denosumab-bbdz J3590
Denosumab-bmwo J3590
Denousmab-bnht Q5158
Denosumab-dssb Q5159
Enoby™ (denosumab- qbde) J3590
Jubbonti® (denosumab-bbdz) Q5136
Jubereq® (denosumab-desu) j3590
Osenvelt® (denosumab-bmwo) Q5157
Ospomyv™ (denosumab-dssb) Q5159
Osvyrti® (denosumab-desu) J3590
Oziltus™ (denosumab-mobz) J3590
Prolia® (denosumab) J0897
Stoboclo® (denosumab-bmwo) Q5157
Wyost® (denosumab-bbdz) Q5136
Xgeva® (denosumab) J0897
Xbryk™ (denosumab-dssb) Q5159
Xtrenbo™ (denosumab-qbde) J3590

Background Information:

- Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor-kB ligand (RANKL). RANKL is a cytokine that is essential for the formation, function, and survival of osteoclasts. By binding RANKL, denosumab prevents the interaction of RANKL with its receptor on osteoclasts and osteoclast precursors and reversibly inhibits osteoclast-mediated bone

resorption. As a monoclonal antibody, denosumab has potential safety risks/significant safety concerns that must be balanced against its potential benefits. Due to its mechanism of action, denosumab presents a novel approach to fracture prevention.

- Bisphosphonates are currently the most predominantly prescribed treatments and have a proven history of safety and efficacy.

- Osteoporosis

    - Approximately 54 million people in the United States have osteoporosis or another form of low bone mass. Breakdown of bone structure may be the result of natural aging and calcium deficiency (e.g., senile osteoporosis) or due to hormonal changes as in post-menopause. The decrease in bone mass and deterioration of bone tissue in osteoporosis can result in bone fragility and potential for fractures. Fractures related to osteoporosis and bone loss are a concern because of the high morbidity and mortality rate and economic burden. The National Osteoporosis Foundation estimates that 1 in 2 women and 1 in 4 men over 50 years of age will break a bone as a result of osteoporosis, resulting in $19 billion in related costs every 2 years and 2 million broken bones.

    - There are numerous randomized controlled trials (RCTs) assessing the efficacy of denosumab. However, only one trial studied the clinically meaningful endpoint of fracture prevention. All other efficacy trials used percent change in bone mineral density (BMD) as the primary endpoint. BMD is a surrogate marker and change in BMD is poorly correlated to fracture prevention. There is one placebo-controlled trial that established the efficacy of denosumab (Prolia) with regard to decreased fracture risk. Denosumab (Prolia) reduces the risk of vertebral, hip, and non-vertebral fractures in post-menopausal women with osteoporosis over 36 months when compared to placebo.

    - Denosumab (Prolia) has not been proven in reliable clinical studies to be more effective than bisphosphonates for treatment of osteoporosis.

    - There are trials comparing denosumab (Prolia) to oral alendronate and IV zoledronic acid for the treatment of osteoporosis in post-menopausal women. The primary endpoint of these trials is BMD changes at 12 and 24 months which is not as clinically relevant as fracture data. One small RCT demonstrated greater osteoporotic fracture reduction for denosumab compared to alendronate; however, future longitudinal studies with longer follow-up and larger sample sizes are needed to confirm the efficacy difference between denosumab and bisphosphonates.

- The FRAX® tool (www.shef.ac.uk/FRAX) was developed by the World Health Organization (WHO) to evaluate fracture risk of patients. It integrates clinical risk factors with BMD at the femoral neck. The FRAX® tool provides the 10-year probability of fracture. The output is a 10-year probability of hip fracture and a 10-year probability of major osteoporotic fracture (forearm, shoulder, or clinical vertebral fracture).

- Treatment should be considered if the 10-year risk is 3% or more for hip fracture or 20% or more for "major" osteoporosis-related fracture based on the US-adapted WHO algorithm (FRAX® tool).

- The American Association for Clinical Endocrinology (AACE)/American College of Endocrinology (ACE) guidelines (2020) define osteoporosis as a BMD T-score at or lower than -2.5. However, a non- or low-traumatic fracture (fragility fracture) is considered osteoporosis regardless of T-score. The AACE guidelines include the following recommendations:

    - AACE/ACE guidelines separate patients with osteoporosis into two categories – high risk or very high risk. Patients who have had a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than − 3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (e.g., major osteoporosis fracture > 30%, hip fracture > 4.5%) or other validated fracture risk algorithm should be considered to be at very high fracture risk. All other patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, are considered to be high risk.

    - The Endocrine Society 2020 Guidelines for the Pharmacological Management of Osteoporosis in Postmenopausal Women separate patients into 4 categories. Their high risk and very high risk categories align with those defined by the AACE/ACE guidelines. However, they also identify patients as low risk if they have no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, a 10-year hip fracture risk < 3%, and 10-year risk of major osteoporotic fractures < 20% or moderate risk when they have no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, and 10-year hip fracture risk < 3% or risk of major osteoporotic fractures < 20%.

    - The AACE recommends either bisphosphonates (IV or oral) or denosumab as initial treatment options for patients with high risk osteoporosis without prior fracture. Guidelines do not give preference to one antiresorptive therapy over another. Bisphosphonates decrease the breakdown of bone and have been shown to increase BMD and reduce the incidence of fractures in patients with osteoporosis. Contraindications to bisphosphonates include hypocalcemia and severe renal impairment. In addition, oral bisphosphonates are contraindicated in patients with the inability to stand or sit upright for at least 30 minutes and may not be an appropriate option in patients with underlying gastrointestinal issues. However, use of IV bisphosphonates is still appropriate in these situations.

- There is evidence to support the superiority of certain antiresorptive agents (Prolia and IV zoledronate) and anabolic agents (Evenity®, Tymlos®, and Forteo®) over oral bisphosphonates for individuals who are unable to use oral bisphosphonates and as initial therapy for individuals with osteoporosis who are considered to be at very high risk for fracture, such as those with a T-score less than -3.0 or those with a history of fracture. These guidelines do not give preference to one therapy over another.

- The Endocrine Society guidelines recommend initial treatment of patients at moderate risk with bisphosphonates (oral or IV) as initial therapy. For patients in the high to very high risk categories, the treatment algorithm recommends bisphosphonates, denosumab, teriparatide, abaloparatide, or romosuzumab all with adjunct calcium and vitamin D therapy as their treatment options.

- Sequential treatment with a bisphosphonate or denosumab (Prolia) is recommended after discontinuation of an anabolic agent to prevent bone density decline and loss of fracture efficacy.

- Until the effect of combination therapy on fracture risk is better understood, the AACE does not recommend concomitant use of FDA approved osteoporosis agents for the prevention or treatment of postmenopausal osteoporosis.

- The goal of monitoring osteoporosis therapy is to identify those who have significant bone loss. AACE recommends a repeat DXA scan 1 to 2 years after initiation of therapy until bone density is stable. Bone turnover markers (BTMs) are also useful for assessing patient compliance and efficacy of therapy. Reductions in BTMs are conferred by antiresorptive therapy and are associated with fracture reduction. Significant increases in BTMs indicate good response to anabolic therapy.

- A drug holiday is not recommended for denosumab (Prolia), and treatment with denosumab should be continued for as long as clinically appropriate. If denosumab therapy is discontinued, patients should be transitioned to another antiresorptive therapy.

- Glucocorticoid-Induced Osteoporosis:

  - A 24-month international, multi-center, double-blind, active-controlled, double-dummy, non-inferiority study compared denosumab to risedronate. Of the 795 patients enrolled, 505 were glucocorticoid-continuing and 290 were initiating therapy.

Denosumab was both non-inferior and superior to risedronate at 12 months for effect on BMD at the lumbar spine in both glucocorticoid-continuing (4.4% [95% CI 3.8–5.0] vs 2.3% [1.7–2.9]; p<0.0001) and glucocorticoid-initiating (3.8% [3.1–4.5] vs 0.8% [0.2–1.5]; p<0.0001) subpopulations. Incidence of adverse events, serious adverse events (including infections), and fractures was similar between treatment groups.

- Guidelines from the American College of Rheumatology (ACR) for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP; 2022) include the following recommendations:

    - A strong recommendation for usage of oral bisphosphonates over no treatment for adults ≥ 40 years old receiving long-term glucocorticoids who are at high or very high risk for fracture.

    - Other agents including IV bisphosphonates, parathyroid hormone/parathyroid hormone related protein (PTH/PTHrP: Foteo or Tymlos), and denosumab are also options that are conditionally recommended. However, ACR notes that the evidence for fracture reduction for denosumab and PTHrP has been demonstrated in general osteoporosis but not GIOP. In addition, ACR states that the denosumab trials were not powered to detect reductions of GIOP fractures and instead use a surrogate endpoint of BMD changes and that the relationship between increases in BMD and a decrease in vertebral fractures is inconsistent.

- Prevention of Osteoporosis Due to Hormone Suppression:

    - In breast and prostate cancer patients on hormone suppression therapy, hormone suppression increases bone turnover and decreases BMD. Oral bisphosphonates are the best value for the prevention of osteoporosis in patients on hormone suppression therapy.

    - There is a limited body of evidence for fracture prevention during hormone suppression therapy. Clinical trials were designed to demonstrate an increase in BMD without evidence of fracture prevention. BMD is a surrogate for fracture risk, the more clinically meaningful measure of efficacy.

    - For prevention of osteoporosis in patients with prostate cancer during androgen deprivation therapy (ADT): there is evidence that denosumab, pamidronate, zoledronic acid, and alendronate increase BMD during ADT. NCCN Prostate Cancer guidelines version 3.2026 (November 7, 2025) recommend (category 2a) denosumab every 6 months, zoledronic acid once annually, or alendronate 70 mg once weekly when risk of fracture warrants treatment. Zoledronic acid increases BMD when administered

every three months OR annually. There is no comparative evidence that demonstrates that more frequent dosing is more effective. One randomized, double-blind prospective study that compared denosumab compared to oral alendronate in 234 male patients undergoing ADT for prostate cancer found that denosumab was associated with a lower rate of new vertebral fractures; however, additional randomized clinical studies are warranted to establish the superiority of denosumab in this clinical setting.

- There is evidence to support the use of antiresorptive agents (bisphosphonates and denosumab) to maintain or improve bone mineral density and reduce the risk of fractures in postmenopausal women who are receiving adjuvant aromatase inhibitor therapy. Therefore, the NCCN Breast Cancer guidelines version 5.2025 (October 16, 2025) recommend bisphosphonate therapy or denosumab as acceptable to maintain or to improve bone mineral density and reduce risk of fracture in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibitor therapy.

- Giant Cell Tumor of Bone (GCTB):

  - Several Phase II trials have examined the efficacy of denosumab for treating primary and recurrent giant cell tumor of the bone (GCTB). In an open-label, Phase II study (N = 37), denosumab induced tumor response (defined as elimination of at least 90% of giant cells or no radiologic progression of the target lesion for up to 25 weeks) in 86% of patients with unresectable or recurrent GCTB.

  - The NCCN Bone Cancer guidelines version 1.2026 (September 11, 2025) recommend denosumab and/or serial embolization as preferred options for patients with lesions that are resectable with unacceptable morbidity and/or unresectable axial lesions. Following primary treatment, patients with stable or improved disease can be observed. Intralesional excision is recommended if the lesion becomes resectable. Patients with unresectable disease should be treated with denosumab, serial embolization, and/or radiation therapy (non-preferred). Guidelines recommend continuation of treatment until disease progression.

- Cancer-Related Bone Metastases:

  - Zoledronic acid (Zometa®) provides the best value for prevention of skeletal complications, decreasing the incidence and rate of skeletal events, and delaying skeletal events in women with breast cancer with bone metastases. The effectiveness of denosumab was evaluated in 7,201 patients with various advanced cancers including metastatic breast, prostate, and various

other solid tumor cancers. There are four RCTs comparing denosumab (Xgeva) with zoledronic acid (Zometa) for the prevention of skeletal-related events (SRE) related to bone metastases.

- SRE related to bone metastases were defined as pathological fractures, spinal cord compression, and bone complications that required radiation or surgery.

- The pooled result demonstrated that denosumab (Xgeva) was significantly superior to zoledronic acid (Zometa) in delaying the time to the first skeletal related event (HR: 0.86; 95% CI: 0.80-0.93; $p < 0.01$), and time to first-and-subsequent SREs (RR: 0.87; 95% CI: 0.81-0.93, $p < 0.01$). However, no significant differences were observed between the two groups in regard to overall survival (OS) or time to disease progression. Additionally, denosumab (Xgeva) was associated with higher incidence of hypocalcemia and osteonecrosis of the jaw (ONJ) compared to zoledronic acid (Zometa). Further analysis is warranted for the comparison of denosumab (Xgeva) and zoledronic acid (Zometa) for advanced cancer with bone metastasis. The NCCN Guidelines for Breast Cancer version 5.2025 (October 16, 2025) recommend denosumab, zoledronic acid or pamidronate (all with calcium and vitamin D supplementation) should be given in addition to systemic therapy or endocrine therapy if bone metastasis is present, expected survival 3 months, and renal function is adequate (category 1).

- Denosumab (Xgeva) extends the time to first SRE by six months in patients with metastatic breast cancer. As a secondary endpoint the number of SREs was reported (number of SREs is the more commonly reported endpoint in efficacy trials). In the metastatic breast cancer trial, 30.7% of denosumab (Xgeva) subjects had an SRE compared with 36.5% of zoledronic acid (Zometa) subjects. This small difference of 5.8%, coupled with the dropout rate of 18% could have influenced the magnitude of difference between the products. It is unclear that that the treatment effect would be as robust if the subjects who left the trial early had completed the trial.

- The claim of superiority in other metastatic solid tumor cancers including prostate cancer is uncertain due to the small treatment effect and high drop-out rates. The drop-out rate (patients who did not complete the trial for reasons other than having an on-study SRE, death or disease progression) was greater than 22% in both trials. Therefore, it is uncertain that study groups remained adequately randomized and balanced by the end of the trials for a fair comparison.

- Prevention of SRE in Patients with Multiple Myeloma (MM)

- A randomized, double blind, active controlled, noninferiority trial compared denosumab and zoledronic acid. It enrolled 1,718 patients with newly diagnosed MM. The study met its primary endpoint. Denosumab was found to be non-inferior to zoledronic acid in delaying the time to first SRE following randomization, with a median time of 22.8 months for denosumab and 24 months for zoledronic acid (HR = 0.98, 95% CI, 0.85-1.14). An SRE was defined as a pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results for overall survival (OS) were comparable between Xgeva and zoledronic acid treatment groups with a hazard ratio of 0.90 (95% CI: 0.70, 1.16).

- The NCCN Guidelines for Multiple Myeloma version 4.2026 (November 26, 2025) recommend bisphosphonates (category 1) or denosumab (category 2a) for all patients receiving therapy for symptomatic MM regardless of documented bone disease. With respect to duration of therapy, the guidelines recommend continuing bone-targeting treatment for up to 2 years and continuing beyond 2 years based on clinical judgement.

- Clinical Efficacy in Hypercalcemia of Malignancy (HCM):

  - HCM is a serious complication that is indicative of poor malignancy prognosis. It results from cancer-driven increases in bone resorption, and if untreated, can lead to renal failure, progressive mental impairment, coma, and death.

  - The classification of severity of hypercalcemia is as follows:

    - Mild hypercalcemia: albumin-corrected serum calcium (CSC) <12 mg/dL

    - Moderate hypercalcemia: albumin CSC between 12 and 14 mg/dL

    - Severe hypercalcemia: albumin CSC >14 mg/dL

  - Denosumab (Xgeva) acts by inhibiting the osteoclast-mediated bone resorption, which results in decrease in bone destruction and calcium release thus lowering calcium levels in HCM patients.

  - The Endocrine Society Guidelines for the Treatment of Hypercalcemia of Malignancy in Adults recommends for adults with sever hypercalcemia a combination of calcitonin and an IV bisphosphonate or denosumab as initial treatment compared with only IV bisphosphonate or denosumab (conditional recommendation). In addition, for adults with moderate to severe

hypercalcemia, they suggest treatment with denosumab over IV bisphosphonate (conditional recommendation) but this recommendation was based on a very low certainty of evidence demonstrating lower incidence of SREs and increased rates of hypocalcemia, both implying higher potency, with denosumab as compared with a BP but that has yet to be confirmed.

- An open-label, single-arm study evaluated 33 patients with advanced cancer and persistent hypercalcemia (CSC of 12.5mg/dL or higher) after recent bisphosphonate treatment. The primary endpoint was the proportion of patients with a response (defined as albumin CSC <11.5 mg/dL within 10 days after the first dose of Xgeva).

- The secondary endpoints included the proportion of patients who experienced a complete response (defined as CSC <10.8 mg/dL by day 10), time to response, and response duration (defined as the number of days from the first occurrence of CSC <11.5 mg/dL).

- Please refer to study results in Table 1 below:

Table 1: Efficacy of Xgeva in Patient with HCM Refractory to Bisphosphonate Therapy

Endpoint	N = 33	Proportion (%)
All Responders (CSC≤ 11.5 mg/dL) by day 10	21	63.6
All Responders by Day 57	23	69.7
Complete Responders (CSC≤ 10.8 mg/dL) by day 10	12	36.4
All Complete Responders by Day 57	21	63.6

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Policy History		
#	Date	Change Description
1.9	Effective Date: 02/12/2026	Added denosumab-desu products Jubereq and Osvyrti, and denosumab-mobz products Boncresa and Oziltus to the policy
1.8	Effective Date: 12/04/2025	Added denosumab-kvqq products Aukelso and Bosaya, added denosumab-qbde products Enoby and Xtenbo, added unbranded Denosumab-bmwo products, and added unbranded Denosumab-bbdz products
1.7	Effective Date: 10/09/2025	Added denosumab-nxxp products Bildyos and Bilprevda to the policy.

1.6	Effective Date: 06/05/2025	Informational update to add Bomyntra, Conexxence and unbranded denosumab-bnht products to the policy.
1.5	Effective Date: 04/10/2025	Added Xbryk, Ospomyv, Stoboclo, and Osenvelt, removed specific timeline for trial of bisphosphonates, and defined what would be considered a failure (such as reduction of T-score or fracture)
1.4	Effective Date: 04/11/2024	Updated to include Jubbonti and Wyost
1.3	Effective Date: 04/06/2023	Updated policy to clarify duration of initial authorization period for Prolia and Xgeva
1.2	Effective Date: 10/06/2022	Shortened duration of bisphosphonate trial to 12 months for osteoporosis indication for Prolia; removed requirement for calcium/vitamin D supplementation for all indications; will not allow for combination therapy with bisphosphonates in addition to anabolic therapies
1.1	Effective Date: 10/07/2021	Annual Review of Medical Policy
1.0	Effective Date: 01/01/2021	New Policy

Eculizumab Products
Bkemv™ (eculizumab-aeeb) Q5139
Epysqli® (eculizumab-aagh) Q5151
Soliris® (eculizumab) J1300

Background Information:

- Soliris is a complement inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis; atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy; generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive; and neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

- Bkemv and Epysqli are biosimilars to Soliris and is indicated for the treatment of PNH to reduce hemolysis and aHUS to inhibit complement-mediated thrombotic microangiopathy. Bkemv is not indicated for the treatment of patients with STEC-HUS.

- Paroxysmal nocturnal hemoglobinuria

- Paroxysmal nocturnal hemoglobinuria is a rare acquired hematopoietic stem cell disorder in which red blood cells undergo cell lysis prematurely mediated by the alternative pathway of complement (APC). PNH arises due to a somatic mutation of a the PIGA gene whose protein product is a glycosyl transferase. Glycosyl transferase is part of the biosynthetic pathway that generates glycosyl phospastidylinositol (GPI) that serves as an anchor for membrane bound proteins on hematopoietic lineage cells. The mutation in PIGA results in a lack of glycosyl transferase activity and near-complete or complete absence of expression of all proteins that are GPI-anchored including the complement inhibitory proteins CD55 and CD59. The deficiency of CD55 and CD59 cause the complement-mediated intravascular hemolysis characteristic of PNH.

- Phenotypic mosaicism of the peripheral blood is a characteristic feature of PNH and is based on quantitative differences in complement sensitivity. Cell complement sensitivity is divided into 3 types. PNH type I cells are defined by having normal sensitivity to complement-mediated lysis. PNH type II cells are moderately complement sensitive or 2 - 4 times more sensitive than normal. Finally, PNH type III cells are markedly complement sensitive or 15 - 25 times more sensitive than normal. Complement sensitivity varies greatly from patient to patient depending on their unique phenotypic mosaicism. Erythrocyte phenotype is clinically relevant as patients with primarily type II cells have a relatively benign clinical course. In contrast, those who have more type III cells, which are completely deficient in CD55 and CD59, will have a more severe clinical course due to increased complement-mediated hemolysis. As Soliris is a complement inhibitor, it was studied only in patients with greater than 10% PNH type III cells on flow cytometry.

- For patients with high disease activity, PNH complications increase significantly. High disease activity is defined as an elevated LDH greater than or equal to 1.5 times the upper limit of normal with constitutional symptoms of weakness, fatigue, hemoglobinuria, abdominal pain, dyspnea, hemoglobin less than 10 g/dL, dysphagia, and erectile dysfunction. Patients with an elevated LDH and at least one additional symptoms should begin treatment with Soliris.

- Thrombolytic complications are the leading cause of morbidity and mortality in PNH. Acute thrombotic events require anticoagulation with heparin. If there is no contraindication, anticoagulation should continue indefinitely for a patient with PNH who has experienced a thromboembolic complication. Soliris has been shown to to reduce the risk of thromboembolic complications and therefore should be initiated if a patient has experienced a thrombotic vascular event. For patients being treated with Soliris and no history of thromboembolic complications, prophylactic anticoagulation may be unnecessary, although it is recommended that anticoagulation continue for those patients who experienced a thromboembolic event prior to initiating therapy with eculizumab.

- Soliris has been shown to decrease the number of blood transfusions required by patients and stabilize hemoglobin levels. It has been studied in patients receiving as few as 1 blood transfusion in 24 months.

- Eculizumab products have not been studied and there is no data to support use in combination with other medications used to treat PNH such as Ultomiris.

- Atypical hemolytic uremic syndrome

- Atypical hemolytic uremic syndrome is an extremely rare disease characterized by hemolytic anemia, thrombocytopenia, and acute kidney failure. Acute presentation may also include neurological findings, including seizures, gastrointestinal symptoms, and cardiovascular involvement, including hypertensive emergency and acute coronory events. Chronic kidney disease (CKD) is the most common long-term complication and may result in the need for dialysis. The signs and symptoms of aHUS result from the formation of microthrombi in various small blood vessels of the body. These clots reduce or prevent proper blood flow to various organs especially the kidneys. Multiple factors, including certain genetic, environmental, and immunologic factors, all play a role in its development.

- The nomenclature and terminology surrounding aHUS can be confusing. Atypical hemolytic uremic syndrome is considered a form of thrombotic microangiopathy (TMA). TMA is broken down into two main forms, thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS).

- TTP is group of syndromes in which patients usually present with thrombocytopenia and microangiopathic hemolytic anemia. Despite similarities in clinical features, the underlying mechanisms of aHUS and TTP differ, altering the manner in which patients respond to different

therapies. TTP results from mutations in the gene encoding a disintegrin and metalloprotease with thrombospondin type 1 motif 13 or ADAMTS13. Patients who are severely ADAMTS13 deficient, defined as ADAMTS13 activity less than 10%, have a confirmed diagnosis of TTP and may not respond to complement-inhibitor therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of TTP and therefore, Soliris should not be prescribed.

- HUS is also broken down into two main forms: aHUS and secondary HUS. Secondary HUS are caused by Shiga toxin E. coli, S. pneumoniae, malignancy, HIV infection, solid organ transplants, hematopoietic stem cell transplants, autoimmune disorders, and the use of certain drugs or medications. HUS caused by infectious bacteria typically presents with diarrhea and responds well to antibiotic therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of infectious HUS and Soliris should not be initiated in these patients. Atypical hemolytic uremic syndrome typically results from complement abnormalities; however, it is a diagnosis of exclusion, meaning the diagnosis is made by excluding other primary thrombotic microangiopathy (TMA) syndromes, such as TTP or infectious HUS.

- Most patients with aHUS present with the complete triad symptoms: hemoglobin less than 10 g/dL, platelets less than 150,000/mm^3, and renal insufficiency with increased serum creatinine or the need for dialysis. The presence of schizocytes, undetectable haptoglobin, and high LDH levels confirm the microangiopathic intravascular origin of hemolysis. Soliris should be initiated in patients with these symptoms and a lack of secondary or infectious causes.

- Eculizumab products have not been studied and there is no data to support use in combination with other medications used to treat aHUS such as Ultomiris.

- Myasthenia gravis

– Myasthenia gravis (MG) is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular, or class I, MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Depending on the severity of muscle weakness, at this point MG is classified as either class II for mild, class III for moderate, and class IV for severe presentation. Those with class V disease require intubation due to profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking.

- Soliris has only been studied and shown to be safe or effective in patients with anti-AChR antibodies. An immunologic assay to detect for the presence of anti-AChR antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has anti-AChR antibodies, at least

one other confirmatory test including a positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) should be conducted.

- The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2020 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery. Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Soliris has not been studied in patients who have undergone thymectomy within 12 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Soliris in these patient populations at this time.

- Standard therapies recommended by the 2020 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, IVIG, and PLEX.

- Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.

- Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporine, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect, doses should be maintained for six months to two years of therapy and then tapered to the lowest effect dose.

- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.

- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose

corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX.

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. A number of case reports and case series support the efficacy of rituximab in patients with refractory MG. In a prospective study of 22 patients with refractory MG treated with rituximab, the mean time to relapse was 17 months. Among 14 patients taking prednisone, the mean daily dose decreased from 25 mg at baseline to 7 mg after treatment with a mean follow-up of 29 months. In an observational study of 72 patients with new-onset or refractory generalized MG, those treated with low-dose rituximab had shorter time to remission, lower use of adjunctive treatments, and fewer adverse events than patients treated with conventional immunosuppressive therapy.

- Soliris should be considered in the treatment of severe, refractory, AChR antibody positive generalized MG. Until further data become available to allow comparisons of cost and efficacy with other treatments guidelines state, Soliris should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals.

    - Soliris has not been studied and there is no data to support use in combination with other medications used to treat MG, such as, Ultomiris, or that one medication is superior to the other.

- Neuromyelitis optica spectrum disorder

    - Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage mainly of the optic nerves and spinal cord. NMOSD is thought to be primarily mediated by the humoral immune system and the autoantibody aquaporin-4 (AQP4) which is released by B-cells and plasma blasts. Serum anti-AQP4 levels have been shown to correlate with disease activity, decrease after immunosuppressive therapy, and remain low during remissions.

    - Soliris is indicated for the treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-AQP4 antibody positive.

    - Safety and efficacy were established in a randomized, double-blind, placebo-controlled trial of 143 patients with NMOSD who were anti-AQP4 antibody positive. The primary endpoint was the time to the first adjudicated on-trial relapse. The primary endpoint was significantly longer in Soliris-treated patients compared to placebo treated patients (relative risk reduction 94%; hazard ratio 0.058; $p < 0.0001$). Soliris-treated patients also had reduced annualized rates of hospitalizations (0.04 for Soliris vs 0.31 for placebo), or

corticosteroid administrations to treat acute relapses (0.07 for Soliris vs 0.42 for placebo), and of plasma exchange treatments (0.02 for Soliris vs 0.19 for placebo).

- Soliris has not been studied and there is no data to support use in combination with other medications used to treat NMOSD, such as Rituxan®, Enspryng, or Uplizna.

- No American treatment guidelines are available for neuromyelitis optica spectrum disorders. The European Federation of Neurological Societies published guidelines for the diagnosis and management of neuromyelitis optica in 2010. Long-term treatment options should be initiated as soon as the diagnosis is made to prevent attacks and reduce the risk of permanent disability, but evidence from randomized-controlled trials for any particular medication is lacking. The guidelines recommend azathioprine plus prednisone or rituximab as first-line therapy to prevent attacks. If first-line treatment is ineffective or the patient develops steroid-dependence for clinical remission, alternative immunosuppressive therapies need to be considered. Second-line therapy includes cyclophosphamide, mitoxantrone, methotrexate, IVIG, mycophenolate mofetil, and intermittent plasma exchange. The guidelines have not been updated to include Uplizna, Soliris, or Enspryng.

- While a variety of immunosuppressive therapy are regarded as first-line therapy based on primarily observational or single-arm data, use has fallen out of favor due to lack of efficacy. The most widely prescribed treatments include azathioprine and mycophenolate mofetil. However, if given, they are often prescribed with low doses of corticosteroids to treat the relapse and the steroids are weaned slowly.

- Rituximab targets the CD20 antigen on B-cells and leads to profound B-cell depletion, principally over an antibody-dependent cell cytotoxicity mechanism and decreases attack frequency and severity in patients with NMOSD. Most of the investigations revealed that Expanded Disability Status Score (EDSS) improved significantly in all patients with rituximab treatment after treatment with rituximab and relapse rates decreased by up to 88%. No new or enlarged lesions or pathological gadolinium enhancement was observed in serial brain and spinal cord MRIs, except for those observed concomitantly with clinical relapses and the median length of spinal cord lesions was significantly reduced after therapy. Paradoxical relapses may occur shortly after initiation of rituximab therapy so it is important to allow enough time for the rituximab to become effective. Complete suppression of CD19-positive B-lymphocytes takes one month.

- There are multiple options for the long-term treatment of NMOSD. There an no clinical trials comparing the efficacy of one therapy to another. Choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability.

- CHAPLE disease

- Complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) disease is an ultra-rare, potentially fatal, inherited autoimmune disorder. It is caused by a lack of CD55 protein and the inability to control complement activity. This leads to damaged blood and lymph vessels in the lower GI tract and a loss of protective immune proteins and blood cells. Patients experience abdominal pain, bloody diarrhea, nausea, vomiting, malabsorption, edema, delayed growth, recurrent lung infections, and blood clots.

- Diagnosis of CHAPLE disease is made based on a combination of factors. Patients will exhibit a clinical history of protein-losing enteropathy (PLE) symptoms, such as hypoalbuminemia and hypogammaglobulinemia. Genetic testing must be performed to confirm a biallelic CD55 loss-of-function mutation on the CD55 gene. Furthermore, patients with CHAPLE disease will have extensive lymphangiectasia upon histological assessment of intestinal biopsy samples or resections.

- Supportive care had been the mainstay and includes anticoagulation therapy, a low-fat medium-chain triglyceride–supplemented diet, supplementation of iron, fat-soluble vitamins, and minerals, use of immunoglobulin replacement therapy for recurrent infections, and albumin infusions. In recent years, Soliris, a C5 complement inhibitor, has been studied and used for CHAPLE disease. It is now considered the treatment of choice due to the results from a clinical trial of 3 patients with CHAPLE disease showing marked clinical improvement with resolution of gastrointestinal symptoms, overall well-being, growth, quality of life, and increases in albumin and total protein levels. In correlation with the clinical improvements, progress was observed in all laboratory outcome parameters including increases in albumin and total protein levels and up to an 80% reduction in membrane attack complex deposition on leukocytes (p-value < 0.001). The progress persisted over 18 months of treatment without any severe adverse events.

- Soliris has not been studied and there is no data to support use in combination with other medications used to treat CHAPLE disease, such as, Veopoz.

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Policy History		
#	Date	Change Description
1.8	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.7	Effective Date: 10/03/2024	Updated to include Epysqli
1.6	Effective Date: 08/08/2024	Updated to include Bkemv and a statement allowing use of Bkemv for all FDA approved indications of the innovator product. The name of the policy was changed from Soliris to the Eculizumab Products Policy
1.5	Effective Date: 06/06/2024	Updated to include a step on Empaveli for the PNH indication
1.4	Effective Date: 10/12/2023	Updated to include CHAPLE disease
1.3	Effective Date: 04/06/2023	Updated to remove the step through Rituxan for the NMOSD indication

1.2	Effective Date: 06/09/2022	Updated to mirror criteria for myasthenia gravis to that of Ultomiris and Vyvgart and to remove prescriber requirements
1.1	Effective Date: 06/10/2021	Update to remove platelet requirement for PNH and the percentage of PNH type III cells required
1.0	Effective Date: 01/01/2021	New Policy

Efgartigimod Products
Vyvgart® (efgartigimod alfa-fcab) J9332
Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) J9334

Background Information:

- Vyvgart is a neonatal Fc receptor blocker indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

- Vyvgart Hytrulo is a combination of efgartigimod alfa, a neonatal Fc receptor blocker, and hyaluronidase, an endoglycosidase, indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive and chronic inflammatory demyelinating polyneuropathy (CIDP).

– Myasthenia Gravis

– Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular, or class I, MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Depending on the severity of muscle weakness, at this point MG is classified as either class II for mild, class III for moderate, and class IV for severe presentation. Those with class V disease require intubation due to profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Vyvgart and Vyvgart Hytrulo have only been studied in patients with class II – IV disease. There is no safety and efficacy data to support use of either drug in patients with class I or V disease at this time.

– Vyvgart and Vyvgart Hytrulo are only indicated for use in patients with anti-AChR antibodies. An immunologic assay to detect for the presence of anti-AChR antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has anti-AChR antibodies, at least one other confirmatory test including a positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) should be conducted.

– The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2021 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery. Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a

surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Vyvgart has not been studied in patients who have undergone thymectomy within 3 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Vyvgart or Vyvgart Hytrulo in these patient populations at this time.

- Safety and efficacy of Vyvgart were established in the ADAPT trial, a randomized, double-blind, placebo-controlled, phase 3 trial of 167 patients with generalized myasthenia gravis regardless of anti-acetylcholine receptor antibody status. Patients had class II – IV disease and were already stable on at least one treatment, which included acetylcholinesterase inhibitors, corticosteroids, or immunosuppressants, for MG prior to study entry. They also had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 indicated they had greater than 50% of symptoms that were non-ocular. Patients were randomly assigned to 10 mg/kg efgartigimod or placebo administered as four infusions per cycle with one infusion given per week repeated as needed depending on clinical response no sooner than 8 weeks after initiation of the previous cycle. The primary endpoint was proportion of acetylcholine receptor antibody-positive patients who were MG-ADL responders defined as a greater than or equal to 2-point MG-ADL improvement sustained for greater than or equal to 4 weeks in the first treatment cycle. The trial met its primary endpoint with 67.7% of efgartigimod-treated acetylcholine receptor-antibody positive gMG patients being responders on the MG-ADL score compared to 29.7% of placebo patients which was statistically significant (p-value < 0.0001).

- Safety and efficacy of Vyvgart Hytrulo were established in the ADAPT-SC trial, a randomized, open-label, parallel-group, phase 3 trial of 110 patients with generalized myasthenia gravis regardless of anti-acetylcholine receptor antibody status. Patients had class II – IV disease and were already stable on at least one treatment, which included acetylcholinesterase inhibitors, corticosteroids, or immunosuppressants, for MG prior to study entry. Patients were randomly assigned to 10 mg/kg Vyvgart or 1,008 mg/11,200 units Vyvgart Hytrulo. The primary endpoint was noninferiority of Vyvgart Hytrulo to Vyvgart. Noninferiority was met (p-value < 0.0001) and Vyvgart Hytrulo demonstrated a mean total IgG reduction of 66.4% from baseline at day 29 compared to 62.2% with Vyvgart. Additional key secondary endpoints were met, which were consistent with efficacy measures from the ADAPT study identifying the correlation between total IgG reduction and clinical benefit in gMG.

- Standard therapies recommended by the 2021 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, rituximab, Soliris®, IVIG, and PLEX.

- Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.

- Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect doses should be maintained for six months to two years of therapy and then tapered to the lowest effective dose.

- Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents that are better supported by randomized clinical trial data.

- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.

- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX. Patients were excluded from the ADAPT trial if they had received IVIG or undergone PLEX 1 month prior to the start of the study.

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. Treatment guidelines state rituximab should be considered as an early therapeutic option in patients with MuSK antibody positive MG who have an unsatisfactory response to initial immunotherapy. The efficacy of rituximab in refractory AChR antibody positives MG is uncertain. It is an option if patients fail or do not tolerate other immunosuppressive agents. Patients were excluded from the ADAPT trial is they had used rituximab 6 months prior to the start of Vyvgart therapy.

- Soliris should be considered in the treatment of severe, refractory, AChR antibody positive generalized MG. Until further data become available to allow comparisons of cost and efficacy with other treatments guidelines state, Soliris should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals. Pateints were excluded from the ADAPT trial is they had received Soliris 6 months prior to the start of Vyvgart therapy.

- Vyvgart and Vyvgart Hytrulo have not been studied and there is no data to support use in combination with other medications used to treat MG, such as, Soliris.

- Chronic Inflammatory Demyelinating Polyneuropathy

- CIDP is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots. It is characterized by a relapsing-remitting or progressive course, glucocorticoid responsiveness, and electrodiagnostic or pathologic features of demyelination. In its classic form, CIDP manifests as a symmetric, motor-predominant neuropathy that results in both proximal and distal muscle weakness. Recognized variants include asymmetric and/or sensory-predominant forms. All share the common pathophysiology of inflammatory demyelination. Although relatively rare, CIDP is important to recognize among the varied causes of polyneuropathy as it is treatable with immunomodulatory therapies.

- There is a temporal continuum between acute inflammatory demyelinating polyneuropathy (AIDP), which is the demyelinating form of Guillain-Barré syndrome (GBS), and CIDP. The time course of progression and the occurrence of relapses are used to distinguish between these entities. GBS commonly reaches its nadir within three to four weeks but does not progress beyond eight weeks. CIDP continues to progress or has relapses for greater than eight weeks. GBS is typically monophasic, but up to two relapses in the first eight weeks from onset can occur. Three or more relapses in the first eight weeks is highly suggestive of acute CIDP. Relapses closer to the eight week time period is more suggestive of CIDP.

- The diagnosis of CIDP should be considered in patients presenting with a progressive or relapsing-remitting polyneuropathy involving both motor and sensory axons along with areflexia, particularly when weakness predominates and affects proximal and distal muscles simultaneously and symmetrically. While the initial suspicion for CIDP is clinical, the diagnosis is confirmed by evidence of peripheral nerve demyelination, which must be demonstrated by electrodiagnostic findings or rarely by nerve biopsy, and exclusion of other disorders that may cause or mimic CIDP.

    - Electromyography (EMG) should be performed in all patients with suspected CIDP and is a critical component of the evaluation. The characteristic electrophysiologic features of a definitive CIDP diagnosis per the EFNS/PNS guidelines are those of peripheral nerve demyelination which include at least one of the following:

    - Greater than or equal to 50% prolongation of motor distal latency above the upper limit of normal in two nerves

    - Greater than or equal to 30% reduction of motor conduction velocity below the lower limit of normal in two nerves

    - Greater than or equal to 20% prolongation of F-wave latency above the upper limit of normal in two nerves or greater than 50% if the amplitude of the distal negative peak compound motor action potention (CMAP) is less than 80% of the lower limit of normal

- Absence of F waves in two nerves, if these nerves have amplitudes of distal negative peak CMAPs greater than or equal to 20% of the lower limit of normal, plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve

- Partial motor conduction block, defined by a greater than 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal, in two nerves, or in one nerve plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve

- Abnormal temporal dispersion, defined by a greater than 30% duration increase between the proximal and distal negative peak CMAP in at least two nerves

- Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in at least one nerve (median greater than or equal to 6.6 ms, ulnar greater than or equal to 6.7 ms, peroneal greater than or equal to 7.6 ms, tibial greater than or equal to 8.8 ms) plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve

- The EFNS/PNS guidelines state probable CIDP is considered when patients have greater than or equal to 30% amplitude reduction of the proximal negative peak CMAP relative to the distal, excluding the posterior tibial nerve, if the distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal in two nerves or in one nerve plus at least one other demyelinating parameter meeting any of the definite criteria in at least one other nerve.

- Cerebrospinal fluid (CSF) analysis is recommended in patients with probable CIDP and particularly for patients in whom the clinical and electrophysiologic findings are inconclusive. Albuminocytologic dissociation is a hallmark of CIDP and represents supportive evidence in the EFNS/PNS diagnostic criteria for probable CIDP.

- Magnetic resonance imaging (MRI) with gadolinium of the spine (including spinal roots, cauda equina), brachial plexus, lumbosacral plexus, and other nerve regions can be used to look for enlarged or enhancing nerves. MRI abnormalities are useful as supportive criteria for probable CIDP in the EFNS/PNS guideline.

– Early administration of effective treatment is important in CIDP. The goal is to stop the immune attack against the myelin sheath of peripheral nerves so that secondary axonal degeneration is minimized. This can improve symptoms and function and can prevent or minimize long-term disability. The treatment approach depends on the severity and course of disease. While some patients with CIDP have such mild disease with minimal impact on function and quality of life that treatment is not required, most patients are significantly impaired and need treatment. Multiple medication trials may be required to optimize treatment response, particularly for patients with severe disease. Serial clinical

examinations are used to monitor for relapses and guide changes in therapy. Once symptoms stabilize, and for patients who present with milder symptoms, the treatment objective is for sustained improvement and to promote remission.

- For most treatment-naïve patients with CIDP who are more than mildly affected or for mildly affected patients who are rapidly worsening, the European Academy of Neurology and Peripheral Nerve Society recommend initial immune-modulatory treatment using either intravenous immune globulin (IVIG), plasma exchange, or glucocorticoids. The initial choice among these therapies is influenced by disease severity, concurrent illness, venous access, treatment side effects, availability, and cost.

- Vyvgart Hytrulo has not been studied and there is no data to support use in combination with other medications used to treat CIDP, such as, immunoglobulin.

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Policy History		
#	Date	Change Description
1.4	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Updated to required self-administration of Vyvgart Hytrulo
1.3	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 08/08/2024	Updated to include the new indication of chronic idiopathic demyelinating polyneuropathy for Vyvgart Hytrulo
1.1	Effective Date: 08/10/2023	Updated to include Vyvgart Hytrulo. Name of the policy was changed from Vyvgart to Efgartigimod Products due to the addition of a second product to the policy
1.0	Effective Date: 05/01/2023	New Policy

Elevidys™ (delandistrogene moxeparvovec-rokl)
HCPCS: J1413

Background Information:

- Duchenne muscular dystrophy (DMD) is a rare, life-limiting, progressive childhood disease that affects 1 in 3,500 – 5,000 live male births. It is characterized by progressive muscle weakness and wasting due to the absence of dystrophin protein that causes degeneration of skeletal and cardiac muscle. Affected individuals are unable to run and jump properly due to proximal muscle weakness of the leg and pelvic muscles. DMD occurs as a result of mutations in the dystrophin gene, located on the X-chromosome, which normally functions to generate dystrophin, a structural protein of muscle cells. Mutations in the dystrophin gene lead to an absence of or a defect in dystrophin protein resulting in the progressive symptoms seen in DMD patients.

- Glucocorticosteroids are the main pharmacologic treatment option used in DMD. The 2018 treatment guidelines for DMD support the use of glucocorticosteroids as they are the only medication currently available to slow the decline in muscle strength and function which in turn reduces the risk of scoliosis and stabilizes pulmonary function. Trials show muscle strength is improved when treated with prednisone at a dose of 0.75 mg/kg daily for up to 6 months. The goal of glucocorticoids in an ambulatory patient is the preservation of ambulation and the minimization of later cardiac, respiratory, and orthopedic complications. Continued treatment after the patient becomes non-ambulatory has shown reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. However, it is important to note that glucocorticosteroids are not able to induce the production of dystrophin-like proteins and therefore do not alter or impact the underlying cause of DMD.

- The exon skipping therapies, including Exondys 51™, Vyondys 53™, Viltepso™, and Amondys 45™, are disease modifying therapies for the treatment of DMD. All were FDA approved under the accelerated approval pathway using a surrogate endpoint of increase in dystrophin in skeletal muscle. There is no evidence the small observed increase in dystrophin from use of these therapies results in a clinically meaningful benefit. Therefore, establishment of a clinical benefit was needed in on-going clinical trials. In 2016, Sarepta launched the phase III ESSENCE trial a confirmatory study comparing Vyondys 53 and Amondys 45 against placebo in nearly 230 patients, looking at the effect these drugs have on timed motor function. The 4-step ascend velocity test, which measures strength and mobility by asking patients to climb four stairs, was conducted and results showed a lack of statistical significance (p-value = 0.309).

- Elevidys is an adeno-associated virus vector-based gene therapy indicated in ambulatory patients at least 4 years of age with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.

- Similar to the exon skipping therapies, Elevidys for ambulatory patients was originally FDA approved under accelerated approval based on expression of Elevidys micro-dystrophin in skeletal muscle observed in patients treated with Elevidys. The FDA granted full approval for ambulatory patients in June 2024 despite the phase III EMBARK trial not meeting primary endpoints and a lack of evidence supporting the small observed increase in dystrophin results in a clinically meaning benefit.

- EMABRK, the phase III, randomized, double-blind, placebo-controlled confirmatory trial, evaluated the efficacy and safety of Elevidys in 120 patients with DMD. The primary endpoint was change in North Star Ambulatory Assessment (NSAA) total score from baseline to week 52 compared to placebo. The trial included stratification of participants by age and baseline NSAA with a minimum of 50% of enrolled patients being age 4 – 5. Patients were eligible if they were on a stable daily dose of oral corticosteroids and had rAAVrh74 antibody titers less than 1:400. Study results showed Elevidys-treated patients improved 2.6 points on their NSAA total score 52 weeks after treatment compared to 1.9 points for those on placebo which was not statistically significant (p-value = 0.24). Secondary endpoints, including change in time to rise (TTR) and the 10-meter walk test, showed statistically significant improvements and were the basis for the director of the FDA's Center for Biologics Evaluation and Research decision to overrule three FDA review teams and two additional directors who opposed the expanded indication and traditional approval for ambulatory patients.

- Multiple groups and individuals at the FDA advised against traditional approval and an expanded indication. A review by FDA statisticians concluded that the collective clinical trial results do not suggest there is substantial evidence to support the effectiveness of Elevidys for the expanded indication to all DMD patients and do not support the conversion of accelerated to traditional approval. An additional joint review from the agency's Clinical and Clinical Pharmacology teams likewise determined that the totality of the data does not provide substantial evidence of effectiveness of Elevidys for treatment of ambulatory DMD patients of any age and that the results argue against expanding access. In a memo, the director of the Office of Clinical Evaluation in the Office of Therapeutic Products (OTP) and the super office director of the OTP, concluded that the clinical results cast significant uncertainty regarding the benefits of treatment of DMD with Elevidys. Furthermore, the two directors found the primary clinical trial endpoint results were not statistically significant and smaller analyses looking at secondary endpoints of specific patient measures, such as, the time it takes patients to rise from the floor or walk 10 meters, were inconclusive, in some cases conflicting, and overall illustrated the unreliability of exploratory analyses to support regulatory decision-making. The director of the Office of Clinical Evaluation in the OTP wrote that they would have recommended Sarepta conduct an additional adequate and well-controlled study of Elevidys in the subgroup(s) of patients for which Sarepta believes the effects of Elevidys to be most promising.

- On June 15, 2025, Sarepta paused the ENVISION trial, its confirmatory study required by the FDA to allow for full drug approval in non-ambulatory patients. ENVISION is investigating the use of Elevidys in older ambulatory and non-ambulatory individuals living with DMD. It includes non-ambulatory patients and ambulatory patients 8 to 18 years old with a primary endpoint of change from baseline in the total score of performance of upper limb (PUL) at week 72. The pause of ENVISION was initiated following a second study participant death due to acute liver failure following Elevidys administration. In November 2025, the FDA required the removal of the indication allowing use in non-ambulatory patients due to reports of fatal acute liver failure in this subpopulation that was treated with Elevidys. In addition to the removal of the indication allowing use in non-ambulatory patients, the FDA required the manufacturer to include a box warning in the prescribing information warning people of the risk of acute severe liver injury and failure. Also a limitation for use was added to the package insert noting Elevidys was not recommended for use in those with preexisting liver impairment (defined as gamma-glutamyl transferase [GGT] greater than 2 time the upper limit of normal or total bilirubin greater than the upper limit of normal not due to Gilbert’s syndrome) or active hepatic viral infection due to the high risk of acute serious liver injury and acute liver failure.

- The plan considers cellular and gene therapies to be proven effective to treat a condition if the following are true: the drug has full Food and Drug Administration approval that was not obtained under the FDA’s accelerated approval pathway and the drug met all of its primary endpoint(s) in its

pivotal trials, or if confirmatory trials were required, the drug met its primary endpoint(s) in its confirmatory trial(s). Cellular and gene therapies that haven't been proven effective (do not meet the listed criteria) are considered a benefit contract exclusion for most plans.

- Based on the current information available, there is insufficient evidence that Elevidys provides a clinical benefit and is safe for use in patients with DMD. Therefore, demonstration of a clinical benefit and safety is warranted in on-going clinical trials.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 02/12/2026	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 08/10/2023	New Policy
1.0	Initial Effective Date: 07/18/2023	New Policy

Empaveli™ (pegcetacoplan)
HCPCS: J3490

Background Information:

- Empaveli is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) and for the reduction of proteinuria in adult and pediatric patients 12 years and older with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN).

- Paroxysmal nocturnal hemoglobinuria (PNH)

  - Paroxysmal nocturnal hemoglobinuria is a rare acquired hematopoietic stem cell disorder in which red blood cells undergo cell lysis prematurely mediated by the alternative pathway of complement (APC). PNH arises due to a somatic mutation of the PIGA gene whose protein product is a glycosyl transferase. Glycosyl transferase is part of the biosynthetic pathway that generates glycosyl phospastidylinositol (GPI) that serves as an anchor for membrane bound proteins on hematopoietic lineage cells. The mutation in PIGA results in a lack of glycosyl transferase activity and near-complete or complete absence of expression of all proteins that are GPI-anchored including the complement inhibitory proteins CD55 and CD59. The deficiency of CD55 and CD59 cause the complement-mediated intravascular hemolysis characteristic of PNH.

  - Phenotypic mosaicism of the peripheral blood is a characteristic feature of PNH and is based on quantitative differences in complement sensitivity. Cell complement sensitivity is divided into 3 types. PNH type I cells are defined by having normal sensitivity to complement-mediated lysis. PNH type II cells are moderately complement sensitive or 2 - 4 times more sensitive than normal. Finally, PNH type III cells are markedly complement sensitive or 15 - 25 times more sensitive than normal. Complement sensitivity varies greatly from patient to patient depending on their unique phenotypic mosaicism. Erythrocyte phenotype is clinically relevant as patients with primarily type II cells have a relatively benign clinical course. In contrast, those who have more type III cells, which are completely deficient in CD55 and CD59, will have a more severe clinical course due to increased complement-mediated hemolysis. There is no guideline recommended cutoffs for when PNH can be diagnosed based on percentage of PNH type III cells.

  - For patients with high disease activity, PNH complications increase significantly. High disease activity is defined as an elevated LDH greater than or equal to 1.5 times the upper limit of normal with constitutional symptoms of weakness, fatigue, hemoglobinuria, abdominal pain, dyspnea, hemoglobin less than 10 g/dL, dysphagia, and erectile dysfunction. Patients with an elevated LDH and at least one additional symptom should begin treatment with Empaveli.

  - Thrombolytic complications are the leading cause of morbidity and mortality in PNH. Acute thrombotic events require anticoagulation with heparin. If there is no contraindication, anticoagulation should continue indefinitely for a patient with PNH who has experienced a thromboembolic complication. Empaveli should be initiated if a patient has experienced a thrombotic vascular event. For patients being treated with Empaveli and no history of thromboembolic complications, prophylactic anticoagulation may be unnecessary, although it is

recommended that anticoagulation continue for those patients who experienced a thromboembolic event prior to initiating therapy with Empaveli.

- Empaveli has been shown to decrease the number of blood transfusions required by patients and stabilize hemoglobin levels. It has been studied in patients receiving as few as 1 blood transfusion in 12 months.

- Empaveli has not been studied and there is no data to support use in combination with other medications used to treat PNH, such as Ultomiris. However, for patients switching from Soliris, Empaveli should be initiated while continuing Soliris at its current dose. After 4 weeks, Soliris should be discontinued before continuing Empaveli monotherapy.

- Complement 3 Glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN):

  - C3G and IC-MPGN are both rare kidney diseases characterized by overactivity of the complement cascade, leading to kidney damage. While sharing similarities, C3G is defined by excessive C3 deposits in the kidney, whereas IC-MPGN involves significant deposits of both C3 and immunoglobulins. Although C3G is a distinct disease from IC-MPGN, the underlying cause and progression of the two diseases are remarkably similar. In both diseases, these deposits in the glomerular basement membrane (GBM) disrupt kidney function. This results in progressive damage to the glomeruli that can lead to kidney failure, requiring patients to go on dialysis or receive a kidney transplant. The estimated incidence for both diseases is approximately 1-4 cases per million population per year. C3G is more commonly diagnosed in childhood, while IC-MPGN can occur at any age, though it is more frequently diagnosed in adults.

  - The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases includes the following treatment recommendations for immunoglobulin- and complement-mediated glomerular diseases with a MPGN pattern of injury:

    - Kidney biopsy is considered the “gold standard” for the diagnostic evaluation of glomerular disease. C3G diagnosis is made when a proliferative histologic lesion with C3 deposition at least 2 orders of magnitude greater than any other immune reactant is seen on immunofluorescence. IC-MPGN is characterized by the deposition of immune complexes containing both polyclonal immunoglobulins and complement. Primary IC-MPGN is also referred to as idiopathic IC-MPGN and indicates that the cause is unknown. Secondary IC-MPGN occurs secondary to infections and certain autoimmune disorders.

    - Guidelines encourage the usual supportive measures including the use of ACEI or ARB to maximally tolerated or allowed daily dose as first-line therapy in treating patients with hypertension and proteinuria as well as those with glomerulonephritis and proteinuria alone.

    - These guidelines have not been updated to include Fabhalta or Empaveli after their label expansions in 2025.

- SGLT2is have been shown to slow renal disease progression in diabetic but also in non-diabetic proteinuric neuropathies as demonstrated in EMPA-KIDNEY and DAPA-CKD. A recent analysis of 148 C3G patient records showed that treatment of these patients often involves a combination of antihypertensive agents and SGLT2i. The use of SGLT2i has increased year-over-year in C3G patients and is also being applied as an earlier line of therapy.

- The safety and efficacy of Empaveli in reducing proteinuria in patients with C3G and IC-MPGN was evaluated in the VALIANT trial. 124 patients were randomized 1:1 to Empaveli or placebo, administered twice weekly as a subcutaneous injection for 26 weeks. Approximately 91% of patients were treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), 72% with immunosuppressants (e.g., mycophenolate mofetil, tacrolimus), 40% with systemic corticosteroids, and 11% with sodium-glucose co-transporter 2 (SGLT2) inhibitors. Use of each of these medications was balanced between the treatment groups. The primary efficacy endpoint was the log-transformed ratio of UPCR (sampled from the first morning urine collections) at week 26 compared to baseline. At week 26, the geometric mean UPCR ratio relative to baseline was 0.33 (95% CI: 0.25, 0.43) and 1.03 (95% CI: 0.91, 1.16) in the Empaveli and placebo groups respectively, resulting in a 68% reduction in UPCR from baseline in the Empaveli group compared to placebo ($p < 0.0001$).

- Empaveli is the first product to be approved for both C3G and IC-MPGN. Fabhalta was approved in March of 2025 for treatment of only C3G in adults.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 02/12/2026	Updated criteria for C3G and IC-MPGN to remove steps on ACE or ARB, SGLT2, and immunosuppressive therapy, as well as requiring use in combination with an ACE or ARB. Added requirement that member must currently be being treated with a maximally tolerated dose of ACE/ARB/or SGTL2
1.4	Effective Date: 10/09/2025	Updated to add new indication and criteria for C3G and IC-MPGN and removed hematologist requirement from PNH criteria to align with other PNH products
1.3	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Empliciti® (elotuzumab)
HCPCS: J9176

Background Information:

- Empliciti is an intravenous monoclonal antibody indicated in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma (MM) who have received one to three prior therapies or in combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

- There are no studies and NCCN guidelines do not support use of Empliciti following failure in a previous line of therapy or after failure of another anti-SLAMF7 monoclonal antibody.

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5.

Policy History		
#	Date	Change Description
1.3	Effective Date: 02/12/2026	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 02/13/2025	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 02/08/2024	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Encelto™ (revakinagene taroretcel-lwey)
HCPCS: J3590

Background Information:

- Macular telangiectasia type 2, also known as MacTel, is the most common form of macular telangiectasia. It is a neurodegenerative metabolic disorder that is correlated with diabetes and coronary artery disease. In MacTel type 2, blood vessels in the macula become dilated and leak fluid, causing swelling and scarring, which can lead to vision loss. Sometimes new blood vessels grow beneath the macula, affecting the macular photoreceptors and causing loss of vision.

- Safety and efficacy were evaluated in two phase III, randomized, multi-center, sham-controlled trials, NTMT-03-A and NTMT-03-B which included 239 patients with MacTel type 2. Participants with ellipsoid zone (EZ; inner segment/outer segment [IS/OS]) loss between 0.16 mm^2 and 2.00 mm^2 were randomly assigned 1:1 to Encelto or sham treatment in the study eye. Patients were included if they had a best corrected visual acuity (BCVA) of 54 letters or better (20/80 or better) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at screening. The primary endpoint was rate of change in EZ area loss from baseline through 24 months. Both clinical trials demonstrated statistically significant change in EZ area loss from baseline which was 56.4% lower in the treatment group compared to the sham group in NTMT-03-A (treatment group: 0.075 mm2, 95% CI: 0.05, 0.10]; sham group: 0.166 mm2, 95% CI: 0.14, 0.19; p-value < 0.0001) and 29.2% lower in NTMT-03-B (treatment group: 0.111 mm2, 95% CI: 0.08, 0.14; sham group: 0.160 mm2, 95% CI 0.13, 0.19; p-value = 0.0186). The proportion of participants with a reduction of 15 early treatment diabetic retinopathy study (ETDRS) letters was similar between treatment groups in both NTMT-03-A (treatment group 13.8% (8/58); sham group 8.8% (5/57); p-value = 0.558) and NTMT-03-B (treatment group 3.4% (2/59); sham group 5.6% (3/54); p-value = 0.669).

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Policy History		
#	Date	Change Description
1.0	Effective Date: 09/01/2025	New Policy

Enjaymo™ (sutimlimab)
HCPCS: J1302

Background Information:

- Enjaymo is a classical complement inhibitor indicated to decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD).

- CAD is a type of autoimmune hemolytic anemia characterized by the premature destruction of RBCs. The antibodies that cause CAD activate hemolysis at cold temperatures, usually 37 to 39° Fahrenheit. Most cases of CAD are due to immunoglobulin M (IgM) antibodies. CAD affects approximately one person per million every year and is prevalent in about 16 people per million. CAD typically develops between the ages of 40 to 80 years. In the United States, the estimated prevalence of primary CAD is around 5,000 cases. Symptoms include fatigue, weakness, pallor, dizziness, palpitations, dyspnea, jaundice, and discoloration of digits, ankles, or wrists.

- Enjaymo is an immunoglobulin G 4 (IgG4) monoclonal antibody that inhibits the classical complement pathway. Inhibition of the classical complement pathway prevents deposition of complement opsonins (extracelluarl proteins that induce phagocytosis) on the surface of RBCs, resulting in inhibition of hemolysis in patients with CAD.

- The First International Consensus Group of experts representing autoimmune hemolytic anemia (AIHA) centers, registries, and study groups have developed recommendations for the diagnosis and management of AIHA (2020). Recommendations includes, but is not limited to, the following:

    - A diagnosis of CAD is defined by chronic hemolysis and a cold agglutinin titer level of ≥64.

    - Patients whose Hgb is >10 g/dL are usually not recommended treatment, except in the presence of significant comorbidities such as ischemic cardiomyopathy and chronic obstructive pulmonary disease that would reduce oxygen delivery to the tissues unrelated to the oxygen-carrying capacity of the blood.

    - For asymptomatic patients, watchful waiting with supportive care only is recommended.

    - For symptomatic patients:

        - First-line treatment: rituximab alone or in combination with bendamustine depending on the severity of CAD and the presence of contraindications to cytotoxic therapies.

        - Second-line treatment: rituximab + bendamustine (if not administered in the first line or if ≥2 years have passed since response to prior combination treatment), rituximab monotherapy (if patient previously responded for ≥1 year) as repeat courses is often effective in relapsed disease.
        - Although there are no randomized trials and no formal approval of any chemoimmunotherapy in CAD, remission after B cell–directed treatment has been confirmed in several systematic studies.
        - Treatment with rituximab + fludarabine or botezomib alone are listed as alternative treatment options. However, use is limited due to toxicity or limited evidence.

    - Treatment goals include, but are not limited to, an increase in hemoglobin levels in patients with symptom-producing anemia, decrease in transfusions or achievement of transfusion independency, resolution of disabling cold-induced circulatory symptoms. All treatment should aim at an improved quality of life.

- Enjaymo was approved in February 2022 based on positive results from a 26-week open label, single arm Phase III study (CARDINAL; NCT03347396) in 24 patients with CAD with a recent history of transfusion. The results showed 54% of participants responded to Enjaymo, defined in the study as a hemoglobin ≥ 12 g/dL or an increase of at least 2 g/dL; patients remaining transfusion-free after week five, and patients did not use other CAD-related treatments.

- As of February 2023, there are now 2.5 years of data available to inform the safety and efficacy of Enjaymo. After completion of the initial 26-week study period in the CARDINAL trial (Part A), participants were allowed to enter the two-year extension period (Part B). 19 out of the 22 original trial participants completed Part B of the open-label study. Results demonstrated that Enjaymo maintained hemoglobin levels higher than 11 g/dL and led to a sustained normalization of hemolysis markers thoughout the study. Additionally, 68% of patients enrolled in Part B remained transfusion-free through the two-year treatment period.

- Enjaymo received an expanded indication in January 2023 to treat hemolysis in adults with CAD without a recent history of transfusion, in addition to its original indication to treat hemolysis in adults with CAD with a recent history of transfusion. Approval of the expanded indication was based on positive results from a 26-week, randomized, placebo controlled Phase III study (CADENZA, NCT03347422) in 42 patients with CAD without a recent history of transfusion. The results showed that 73% and 15% of participants who received Enjaymo and the placebo, respectively, achieved the primary endpoint, defined as an increase in hemoglobin from baseline by at least 1.5 g/dL at Weeks 23, 25 and 26, and the absence of blood transfusions and avoidance of CAD medications from Week 5 to Week 26 of the study.

- Enjaymo offers a novel mechanism of action, substantial efficacy, and a favorable safety profile for adults with CAD. Without long term data and data comparing it to use of the guideline-recommended options with an established track record of safety and efficacy along with the probable need for indefinite treatment duration, it is unknown whether Enjaymo is a superior treatment option at this time.

References:

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Policy History		
#	Date	Change Description
1.3	Effective Date: 04/10/2025	Annual review – no changes made to existing criteria
1.2	Effective Date: 04/11/2024	Annual review – No changes made to existing criteria
1.1	Effective Date: 04/06/2023	Annual review – No changes made to existing criteria
1.0	Effective Date: 02/01/2023	New policy

Entyvio® IV (vedolizumab)
HCPCS: J3380

Background Information:

- Entyvio is an integrin receptor antagonist indicated for:

- Adults with moderately to severely active ulcerative colitis (IV/subcutaneous)

- Adults with moderately to severely active Crohn's disease (IV only)

- Crohn's disease (CD)

- The 2018 American College of Gastroenterology (ACG) guidelines establish therapeutic recommendations for patients with CD based upon disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Current therapeutic approaches should be considered a sequential continuum to treat acute disease or induce clinical remission and then to maintain response/remission. In general, clinical evidence of improvement should be evident within 2 – 4 weeks and the maximal improvement should occur within 12 – 16 weeks. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease, have their medication dose adjusted in order to attempt to optimize therapy, or advance to treatment for moderate to severe disease according to their clinical status.

- Corticosteroids are used primarily for the treatment of flares of CD. Conventional corticosteroids are effective for reducing the signs and symptoms of active CD and induction of remission in patients with moderately to severely active CD. Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active disease. The ACG guidelines recommend prednisone equivalent doses ranging from 40 to 60 mg per day. These doses are typically maintained for 1 –2 weeks and tapered at 5 mg weekly until 20 mg and then 2.5 –5 mg weekly. Once begun, care should be taken to ensure that corticosteroids are successfully discontinued, and steroid-sparing agents should be used.

- In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, mercaptopurine, azathioprine, and intramuscular or subcutaneous methotrexate are effective as steroid-sparing agents and are recommended by the guidelines. Maximum effectiveness of these agents can be seen between 8 to 12 weeks from therapy initiation. Methotrexate is also recommended in combination with steroids as effective for treatment of moderately active steroid-dependent/resistant CD. Cyclosporine, tacrolimus, and mycophenolate are not recommended for treatment of CD.

- Biologics, such as anti-tumor necrosis factor (anti-TNF) agents are recommended to treat CD that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. The ACG guidelines also recommend the use of biologics in combination with immunosuppressants to help decrease the formation of antibodies against the biologic therapy. There are no robust, published studies to support use of biologic agents in combination.

- Entyvio is indicated for moderate to severely active disease; however, it only has proven efficacy in adults with moderate to severely active CD who had an inadequate response, lost response, or where intolerant to anti-TNF agents, immunomodulators, or corticosteroids.

- The 2021 American Gastroenterological Association (AGA) guidelines include similar recommendations for the management of moderate-to-severe CD compared to the recommendations cited in the 2018 ACG guidelines. Both guidelines recommend corticosteroids over no treatment for induction of remission. Additionally, both guidelines recommend thiopurines, such as azathioprine or 6-mercaptopurine, as steroid-sparing agents for maintenance of remission. The AGA guidelines also recommend the same biologic agents cited in the ACG guidelines for treatment of CD, with the exception of Tysabri® (natalizumab), which the AGA suggests against due to its associated risk of progressive multifocal leukoencephalopathy (PML).

- Of note, the AGA guidelines conditionally recommend earlier introduction of biologic therapy prior to failure of corticosteroids; however, this recommendation is supported by a low level of clinical evidence. To date, no blinded randomized controlled trials (RCTs) have demonstrated the superiority of early introduction of biologic therapy compared to conventional induction therapy with corticosteroids followed by steroid-sparing therapy. The 2021 AGA guideline authors also acknowledge that earlier therapy with either combination immunomodulator plus biologic therapy or biologic monotherapy may result in over-treating some patients and potentially exposing them to treatment-related risks and costs with limited benefit.

- Ulcerative Colitis (UC)

- The 2019 American College of Gastroenterology guidelines and the 2020 American Gastroenterology Association guidelines state therapeutic management in UC should be guided by the specific diagnosis, an assessment of disease activity, and disease prognosis. Treatment selection should be based not only on inflammatory activity but also on disease prognosis.

- Remission can be induced using a variety of medications, including, oral 5-aminosalicylates (5-ASA), corticosteroids, or biologic agents. In patients with mild to moderately active disease, treatment with 5-ASA therapy has proven to be safe and efficacious for induction. Recommended dosing is 2 grams per day of oral 5-ASA or at least 1 gram per day of rectal 5-ASA with improvement usually seen within 4 weeks. A typical treatment course may be up to 8 weeks.

- Oral steroids are recommended for induction for patients with severe disease or those who did not respond to 5-ASA therapy. The typical starting doses of oral prednisone are 40 – 60 mg per day, and clinical response is expected within 5 – 7 days of treatment. A typical treatment course with oral prednisone is 14 days. The duration of systemic corticosteroids should be as short as possible with early initiation of steroid-sparing therapy. The speed of the taper should be guided by clinical symptoms, cumulative steroid exposure, and onset of action of alternate therapies. Those unable to taper off 10-20 mg of prednisone per day without relapsing are considered steroid dependent. Use systemic corticosteroids for maintenance of remission is not recommended.

- Thiopurines, such as azathioprine and mercaptopurine, can be used to maintain remission. Guidelines recommend use of thiopurines over no medication or corticosteroids for maintenance therapy. Thiopurines are slow acting with maximum effectiveness of these agents being seen between 8 to 12 weeks from therapy initiation. They do not induce remission in moderately to severely active UC. Similarly, methotrexate is not an effective induction agent for induction or maintenance of remission.

- Entyvio is also recommended for patients with moderate to severe disease with prior failure of anti-TNF therapy. Xeljanz® is recommended for patients with moderate to severe UC only after failure of, or intolerance to, anti-TNF agents.

References:

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Policy History		
#	Date	Change Description
1.5	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Added criteria requiring member to self-administer unless clinically unable to do so
1.4	Effective Date: 10/03/2024	Added "for the same indication" to the not to be used in combination with other biologics or targeted DMARDs criteria

1.3	Effective Date: 12/14/2023	Updated to include Entyvio SQ, FDA approved indication, and update the trial and failure preferred verbiage to reference pharmacy and medical benefit
1.2	Effective Date: 12/01/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 12/09/2021	Removed FDA approved indications criteria
1.0	Effective Date: 01/01/20121	New Policy

Enzyme Replacement Therapy for Fabry Disease
Elfabrio® (pegunigalsidase alfa-iwxj) J0180
Fabrazyme® (agalsidase beta) J2508

Background Information:

- Fabry's disease (FD) is autosomal recessive lysosomal storage disorder caused by a mutation on the GLA gene. It is characterized by lysosomal accumulation of undegraded glycosphingolipid due to a deficiency or insufficient activity of the enzyme α-galactosidase. Phenotypes vary from the "classic" phenotype, with pediatric onset and multi-organ involvement, to later-onset, a predominantly cardiac phenotype. While it was once thought females were asymptomatic carriers, it is now known they can develop a variety of symptoms later in life than their homozygous male counterparts. The most common symptoms include hearing loss, myocardial microvascular ischemia, dysrhythmias, hypertrophic cardiomyopathy, valvular insufficiency, gastrointestinal symptoms, hypohidrosis, temperature and exercise intolerance, dysregulation of vascular tone and autonomic functions, obstructive lung disease, progressive renal insufficiency leading to kidney failure, and increased risk of cerebrovascular accidents and myocardial infarctions.

- The American College of Medical Genetics 2011 guidelines state FD is confirmed differently for males and females. Males should first be tested for reduced α-galactosidase activity in peripheral leukocytes or skin fibroblasts. If the enzyme activity test comes back with decreased activity, disease is then verified though genetic testing that shows the patient has a mutation of the GLA gene. Enzyme activity does not often correlate to disease symptoms or severity in heterozygous females. Therefore, when confirming disease in female patients, enzyme activity testing can be waived and genetic testing completed as the initial and only required diagnostic component.

- Enzyme replacement is the standard of care in FD. Fabrazyme is approved for patients aged 2 years and older with FD. Elfabrio is approved for adult patients with confirmed FD.

- There are no uniform recommendations as to when enzyme replacement therapy (ERT) should be started. Typically, males who present with classic disease should be started on prophylactic ERT at time of diagnosis even if they are not presenting with symptoms. Classic disease has little to no enzyme activity on serum assay (< 1% of the normal mean) with symptoms presenting as listed above. For female carriers and males with atypical disease, ERT should be held until patients become symptomatic. There is no data showing benefit of prophylactic therapy in these patients and some will not develop any disease manifestations.

- Fabrazyme, Elfabrio, and Galafold®, a pharmacological chaperone, have not been studied in any combination and there is no clinical data to support better patient outcomes with use of any of the drugs at the same time.

References:

1. Fabrazyme [prescribing information]. Cambridge, MA: Genzyme Corporation; July 2024.
2. Elfabrio [prescribing information]. Cary, NC: Chiesi USA, Inc.; June 2024.
3. Galafold [prescribing information]. Cranbury, NJ: Amicus Therapeutics U.S., Inc.; October 2024.
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Policy History		
#	Date	Change Description
1.6	Effective Date: 08/07/2025	Updated to remove the step through Fabrazyme prior to Elfabrio
1.5	Effective Date: 06/05/2025	Annual review – no changes to the criteria at this time
1.4	Effective Date: 06/06/2024	Annual review – no changes to the criteria at this time
1.3	Effective Date: 06/08/2023	Updated to include Elfabrio and changed the name from Fabrazyme to Enzyme Replacement Therapy for Fabry Disease
1.2	Effective Date: 10/06/2022	Annual review – no changes to the criteria at this time

1.1	Effective Date: 10/07/2021	Annual review of policy. No changes were made to the criteria
1.0	Effective Date: 01/01/2021	New Policy

Enzyme Replacement Therapy for Gaucher's Disease
Cerezyme® (imiglucerase) J1786
Elelyso® (taliglucerase) J3060
Vpriv® (velaglucerase alfa) J3385

Background Information:

- Gaucher's disease (GD) is an autosomal recessive lysosomal storage disorder caused by a mutation on the gene glucocerebrosidase 1. It is characterized by lysosomal accumulation of undegraded glucosylceramide due to a deficiency or insufficient activity of the enzyme glucocerebrosidase. There are three main disease variants with type 1 being considered non-neuronopathic and the least severe. Signs, symptoms, and severity vary greatly among patients with type 1 GD. The most common symptoms include anemia, thrombocytopenia, bone disease, including bone abnormalities and osteopenia/osteoporosis, and hepatosplenomegaly.

- The American College of Medical Genetics 2011 guidelines state Gaucher's disease is confirmed through identifying reduced glucocerebrosidase activity in peripheral leukocytes or skin fibroblasts and through genetic testing that shows the patient has two pathogenic mutations of the glucocerebrosidase gene.

- Enzyme replacement is the standard of care in GD. Three enzyme replacement therapies are FDA approved for long-term enzyme replacement in type 1 Gaucher's disease: Cerezyme, Elelyso, and Vpriv. Elelyso and Vpriv are approved for patients aged 4 years and older and Cerezyme for patients 2 years and older. Guidelines do not recommend the use of one enzyme replacement therapy over another.

- Treatment should be initiated when two of the following symptoms are present: hepatomegaly, splenomegaly, interstitial lung disease, pulmonary hypertension, anemia, thrombocytopenia, bony pain crisis, osteopenia, aseptic necrosis of the femoral head, bony lytic lesions, bony infarctions, or pathologic fractures. Symptom improvement is typically seen within 1 year from the start of therapy for major peripheral symptoms. Bone abnormalities may take up to several years to respond to therapy.

- Decisions regarding dose management should be made by physicians who are experienced in caring for patients with Gaucher's disease with the deciding factor for dosing being the achievement of therapeutic goals. Dose reductions can occur once significant improvements are achieved and maintained for at least a year. Patients with severe manifestations are not recommended to have dose reductions after initial improvement. Adult patients at increased risk who have achieved all therapeutic goals can have the dose decreased in small increments (approx. 15% - 20%) until their next scheduled evaluation in 3 - 6 months. These adult patients and all children are not recommended to have a long-term maintenance dose less than 30 U/kg every 2 weeks. Lower-risk adult patients may tolerate larger dose reductions of 25% - 50% per dose. The minimum long-term dose for lower-risk adults is recommended to be no less than 20 U/kg every 2 weeks.

References:

1. Cerezyme [prescribing information]. Cambridge, MA: Genzyme Corporation; July 2024.
2. Elelyso [prescribing information]. New York, NY: Pfizer, Inc.; July 2024.
3. Vpriv [prescribing information]. Lexington, MA: Shire Human Genetic Therapies, Inc.; July 2024.
4. Weinreb N et al. A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase. Am J Hematol. 2008; 83(12): 890-95.
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Policy History		
#	Date	Change Description
1.5	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 10/03/2024	Annual review – no changes to the criteria at this time
1.3	Effective Date: 10/12/2023	Updated to remove prescriber requirements
1.2	Effective Date: 10/06/2022	Annual review – no changes to the criteria at this time
1.1	Effective Date: 10/07/2021	Annual review – no changes to the criteria at this time
1.0	Effective Date: 01/01/2021	New Policy

Enzyme Replacement Therapy for Mucopolysaccharidosis (MPS)
Aldurazyme® (laronidase) J1931
Elaprase® (idursulfase) J1743
Mepsevii™ (vestronidase alfa-vjbk) J3397
Naglazyme® (galsulfase) J1458
Vimizim™ (elosulfase alfa) J1322

Background Information:

- The mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs). All of the MPS subtypes are autosomal recessive disorders, with the exception of MPS II, which is X linked. The phenotype of these disorders covers a broad spectrum, from mild to severe. In general, the severity depends upon the quantity of residual enzyme, which is related to the genotype of the affected patient. The MPS disorders are differentiated clinically by their clinical features and age of presentation and biochemically by their associated enzyme deficiency.

- MPS type I (Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome)

    - MPS type I is autosomal recessive lysosomal storage disorder caused by a mutation on the gene IDUA. It is characterized by lysosomal accumulation of undegraded heparan and dermatan sulfate due to a deficiency or insufficient activity of the enzyme α-L-iduronidase. There are three main disease variants: Hurler, the most severe with early onset and neurocognitive regression, Hurler-Scheie, the form with intermediate onset and severity, and Scheie, the most mild of the subtypes. Signs, symptoms, and severity vary greatly among MPS type I patients. The most common symptoms include hepatosplenomegaly, hernias, neurocognitive and developmental issues in the more severe forms, cervical spinal cord compression, corneal clouding, open-angle glaucoma, valvular dysplasia and insufficiency, carpal tunnel, short stature, and osteopenia/osteoporosis.

    - The American College of Medical Genetics 2011 guidelines state MPS type I is confirmed through serum assay showing a decrease of α-L-iduronidase activity. Once shown the patient has a decrease in enzyme activity, a genetic test should be performed which should show a mutation in the IDUA gene. Both tests must be demonstrative of disease for the diagnosis to be confirmed.

    - Enzyme replacement (ERT) and stem cell transplant (SCT) are the only treatment options for MPS type I. Aldurazyme is the only FDA approved enzyme replacement therapy for MPS type I. It is approved for adult and pediatric patients with Hurler and Hurler-Scheie forms of MPS type I and for patients with the Scheie form who have moderate to severe symptoms. ERT should be initiated on the judgement of the treating physician and can be held in milder disease until a more significant clinical picture presents. If patients are found to have severe disease or be at risk for neurocognitive decline, they should be assessed for SCT. Patients should be reassessed every 3 months

and if the physician starts to see developmental delays, skeletal manifestations, or severe organomegaly SCT should be considered at that time.

- MPS type II (Hunter syndrome)

    - MPS type II is a X-linked recessive lysosomal storage disorder caused by a mutation on the I2S gene. It is characterized by lysosomal accumulation of undegraded heparan and dermatan sulfate due to a deficiency of the enzyme iduronate-2-sulfatase. Signs, symptoms, and severity can vary greatly among MPS type II patients due to the multisystem nature of the disease. The most common symptoms include coarsened facial features, an enlarged head, an enlarged tongue, hypertrophic tonsils and adenoids, irregularly shaped teeth, recurrent otitis media, hepatosplenomegaly, abdominal and/or inguinal hernias, thickened pebbled skin, and short stature.

    - The American College of Medical Genetics 2011 guidelines state MPS type II should be confirmed through serum assay showing a decrease of iduronate-2-sulfatase activity. Once shown the patient has a decrease in enzyme activity, a genetic test should be performed which should show a mutation in the I2S gene. Both tests must be demonstrative of disease for the diagnosis to be confirmed.

    - Enzyme replacement is the standard of care in MPS type II. Elaprase the only FDA approved ERT for patients with MPS type II. Safety and efficacy have not been established in patients younger than 16 months of age. Initiation of ERT should be done based on the judgement of the treating physician and parents should be counselled on the inability to reverse the cognitive deficits of the disease.

- MPS type IVA (Morquio A syndrome)

    - MPS type IVA is a autosomal recessive lysosomal storage disorder caused by a mutation on the GALNS gene. It is characterized by lysosomal accumulation of keratan sulfate and chondroitin-6-sulfate due to a deficiency of the enzyme N-acetyl-galactosamine-6-sulfatase. Symptoms include growth delays, a prominent lower face, kyphoscoliosis or concern for a spine abnormality, an abnormally short neck, knees that are abnormally close together, flat feet, abnormal development of the growing ends of the long bones, hip dislocation, arthritis, and/or a prominent breast bone.

    - MPS type IVA diagnosis is suggested by the findings of medical history, physical examinations, skeletal X-rays, and urine GAG analysis. Excessive amounts of keratan sulfate will usually be present in the urine. Diagnosis is confirmed by low N-acetyl-galactosamine-6-sulfatase activity in cultured blood or skin cells and/or molecular genetic testing to identify *GALNS* gene mutations.

    - Vimizim is the only FDA approved ERT for patients with MPS type IVA. Safety and efficacy have not been established in patients younger than 5 years of age. Initiation of ERT should be done based on the judgement of the treating physician. All other therapies are symptomatic and supportive.

- MPS type VI (Maroteaux-Lamy syndrome)

- MPS type VI is a autosomal recessive lysosomal storage disorder caused by a mutation on the ARSB gene. It is characterized by lysosomal accumulation of undegraded dermatan sulfate due to a deficiency of the enzyme N-acetylgalactosamine-4-sulfatase. Age of presentation and velocity of disease progression are variable, but affected patients typically come to medical attention at 6 – 24 months of age. The most common symptoms include deceleration of growth velocity, macrocephaly, macroglossia, facial coarsening, hepatosplenomegaly, progressive corneal clouding, open-angle glaucoma, skeletal abnormalities, painful hip dysplasia, restriction in joint mobility, cardiac valvular dysfunction, recurrent otitis media, conductive hearing loss, and upper airway obstruction.

- The American College of Medical Genetics 2011 guidelines state MPS type VI should be confirmed through serum assay showing a decrease of N-acetylgalactosamine-4-sulfatase activity. Once shown the patient has a decrease in enzyme activity, a genetic test should be performed which should show a mutation in the ARSB gene. Both tests must be demonstrative of disease for the diagnosis to be confirmed.

- Enzyme replacement (ERT) and stem cell transplant (SCT) are the only treatment options for MPS type VI. Naglazyme is the only FDA approved enzyme replacement therapy for MPS type VI. It has been studied in patients 3 months of age and older. Families should be counselled on both treatment choices. If ERT is the modality of choice, it should be started immediately.

- MPS type VII (Sly syndrome)

- MPS type VII is a autosomal recessive lysosomal storage disorder caused by a mutation on the GUSB gene. It is characterized by lysosomal accumulation of undegraded dermatan sulfate, chondroitin-4,6-sulfate, and heparan sulfate due to a deficiency of the enzyme β-glucuronidase. Signs, symptoms, and severity can vary among MPS type VII patients. The most severe cases are characterized by hydrops fetalis which can result in stillbirth or death shortly after birth. More mild cases start to present in early childhood with the most common symptoms including short trunk, growth disability, short trunk dwarfism, macrocephalic head, short neck, dysostosis multiplex, coarse facial appearance, cloudy corneas, developmental delays in language and speech, hepatosplenomegaly, hearing loss, hernias, thickening of the soft tissues of the throat, abnormally large tongue, and heart problems.

    - MPS type VII diagnosis is suggested by the findings of medical history and urine GAG analysis. Excessive amounts of dermatan sulfate, chondroitin-4,6-sulfate, and heparan sulfate will usually be present in the urine. Diagnosis is confirmed by low β-glucuronidase activity in cultured blood or skin cells and/or molecular genetic testing to identify GUSB gene mutations.

- Mepsevii is the only FDA approved ERT for use in pediatric and adult patients for the treatment of MPS type VII. Safety and efficacy have been established in patients younger than 18 months of age. All other therapies are symptomatic and supportive.

References:

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3. Vimizim [prescribing information]. Novato, CA: BioMarin Pharmaceuticals, Inc.; December 2019.
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Policy History		
#	Date	Change Description
1.5	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 10/03/2024	Annual review – no changes to the criteria at this time
1.3	Effective Date: 10/12/2023	Updated to remove prescriber requirement
1.2	Effective Date: 10/06/2022	Annual review – no changes to the criteria at this time
1.1	Effective Date: 10/07/2021	Annual review – no changes to the criteria at this time
1.0	Effective Date: 01/01/2021	New Policy

Enzyme Replacement Therapy for Pompe Disease
Lumizyme® (alglucosidase alfa) J0221
Nexviazyme® (avalglucosidase alfa-ngpt) J0219
Pombiliti™ (cipaglucosidase alfa-atga) J1202

Background Information:

- Pompe disease (PD) is an autosomal recessive lysosomal storage disorder caused by a mutation on the GAA gene. It is characterized by lysosomal accumulation of undegraded glycogen due to a deficiency or insufficient activity of the enzyme acid α-glucosidase. All patients with PD have variable but progressive, skeletal, heart, and smooth muscle issues with resulting organ damage and ultimately organ failure. The disease is classified as either infantile-onset or late-onset. Patients with infantile-onset PD present around 3 months of age with progressive left ventricular hypertrophy and generalized muscular hypotonia and typically die within the first year of life because of cardiorespiratory failure. They may also experience macroglossia, hepatosplenomegaly, and feeding difficulties. Late-onset PD can present at any age and is characterized by a slowly progressive myopathy predominantly involving skeletal muscle. Symptoms include progressive muscle weakness of the proximal lower limbs and the paraspinal muscles, respiratory failure, frequent upper airway infections, orthopnea, sleep apnea, and morning headaches.

- The American College of Medical Genetics 2011 guidelines state Pompe disease is confirmed through serum assay showing a decrease of acid α-glucosidase enzyme activity. Once shown the patient has a decrease in enzyme activity, a genetic test should be performed which should show a mutation in the GAA gene. Both tests must be demonstrative of disease for the diagnosis to be confirmed.

- Enzyme replacement therapy (ERT) is the standard of care in PD. Lumizyme, Nexviazyme, and Pombiliti are the ERT's approved for use in PD. While Lumizyme is approved for both infantile-onset and late-onset disease, Nexviazyme and Pombiliti are only indicated for use in late-onset PD. Pombiliti must be used in combination with Opfolda and only after the patient has not had improvement on their current ERT.

- Initiation of therapy should begin at the time of diagnosis for patients with infantile disease. ERT can be held in late-onset patients with patients being observed every 6 – 12 months until the time the monitoring physician feels it is appropriate to start therapy. Studies have been conducted assessing the efficacy of ERT on cardiac symptoms in late-onset patients. Cardiovascular parameters were not impacted by use of ERT and therefore should not be the only presenting symptom when therapy is started.

References:

1. Lumizyme [prescribing information]. Cambridge, MA: Genzyme Corporation; March 2024.
2. Nexviazyme [prescribing information]. Cambridge, MA: Genzyme Corporation; September 2023.
3. Pombiliti [prescribing information]. Philadelphia, PA: Amicus Therapeutics US, LLC; July 2024.

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8. Schoser B, Roberts M, Byrne BJ, et al. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial. Lancet Neurol. 2021 Dec; 20 (12): 1027 - 37.

Policy History		
#	Date	Change Description
1.6	Effective Date: 12/04/2025	Annual review of criteria was performed, no changes were made
1.5	Effective Date: 12/12/2024	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 12/14/2023	Updated to include Pombiliti
1.3	Effective Date: 10/12/2023	Updated to remove prescriber requirement
1.2	Effective Date: 10/06/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 10/07/2021	Updated to include Nexviazyme and name changed from Lumizyme to the Enzyme Replacement for Pompe Disease Policy
1.0	Effective Date: 01/01/2021	New Policy

Epkinly™ (epcoritamab-bysp)
HCPCS: J9321

Background Information:

- Epkinly is a bispecific CD20-directed CD3 T-cell engager 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 after two or more lines of systemic therapy, adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy, and in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory FL.

- Safety and efficacy were evaluated in the EPCORE NHL-1 study, an open-label, multi-cohort, multicenter, single-arm trial in 157 patients with relapsed or refractory large B-cell lymphoma (LBCL) and 127 patients with relapsed or refractory FL after two or more lines of systemic therapy, which included at least one therapy containing an anti-CD20 monoclonal antibody. Patients were required to have failed at least two prior lines of therapy one of which was an anti-CD20 antibody containing regimen. Subjects also must have either failed prior autologous hematopoietic stem cell transplantation (HSCT) or be ineligible for autologous stem cell transplantation due to comorbidities or age, have CD20 positive disease, measurable disease, and an ECOG score of 0 – 2. Those who had a prior allogenic stem cell transplant were ineligible for study inclusion. Patients were also excluded from the trial if creatinine clearance was greater than 45 mL/min; alanine aminotransferase was less than 3 times the upper limit of normal; they had known active CNS involvement of lymphoma; there was an infection that was uncontrolled or required IV or long-term oral antimicrobial therapy; or they could not have HIV infection or hepatitis B or C virus infection if the viral load was detectable. Those with myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months of study entry were not enrolled in the trial. The primary outcomes were overall response rate (ORR) and duration of response (DOR). Overall response rate in patients with relapsed or refractory DLBCL was 68% (95% CI: 45, 86), with 45% achieving a complete response. The median time to response was 1.4 months (range: 1 to 8.4 months). Among responders, the median follow-up for DOR was 9.8 months (range: 0.0 to 17.3 months). In those with FL, the OOR was 82% (95% CI: 74.1, 88.2) with 60% achieving a complete response. The median follow-up for DOR was 14.8 months with over half of the patients remaining responsive to treatment.

- Safety and efficacy were also evaluated in the EPCORE FL-1 study, an open-label, randomized, multicenter trial 488 patients with relapsed or refractory FL after at least one line of systemic therapy which included an anti-CD20 antibody containing regimen. Subjects must have CD20 positive disease, measurable disease, and an ECOG score of 0 – 2. The primary endpoints were progression free survival (PFS) and ORR. The study demonstrated superiority of PFS and ORR in the Epkinly arm. The PFS hazard ratio was 0.21 (95% CI: 0.13, 0.33; p-value < 0.0001). The median PFS was not reached (95% CI: 21.9 months, NR) in the Epkinly arm and was 11.2 months (95% CI: 10.5, NR) in the control arm. The ORR was 89% (95% CI: 84, 93) in the Epkinly arm and 74% (95% CI: 68, 79) in the control arm.

- Due to the risk of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS), Epkinly should be administered in an inpatient setting during cycle 1, day 15.

- Epkinly has not been studied when given following prior treatment with Epkinly or following any other bispecific CD20-directed CD3 T-cell engager therapy.

References:

1. Epkinly [prescribing information]. Plainsboro, NJ: Genmab US, Inc.; November 2025.
2. Hutchings M, Mous R, Roost Clausen M, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021 Sept 8; 398 (10306): 1157 – 69.
3. Clinicaltrials.gov. Study of subcutaneous epcoritamab in combination with intravenous rituximab and oral lenalidomide (R2) to assess adverse events and change in disease activity in adult participants with follicular lymphoma (EPCORE FL-1) (NCT05409066). Available at: https://clinicaltrials.gov/study/NCT05409066#participation-criteria. Accessed on December 1, 2025.
4. National Comprehensive Cancer Network. B-cell lymphomas (Version 3.2025). 2025 August 18. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed on December 1, 2025.

Policy History		
#	Date	Change Description
1.4	Effective Date: 02/12/2026	Updated to include the new FDA approved indication for use in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma
1.3	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/03/2024	Updated to remove the following requirements: failure of prior autologous HSCT or be ineligible for autologous stem cell transplantation due to comorbidities or age, measurable disease, ECOG status, kidney function; liver function, no prior allogenic SCT, no known active CNS involvement of lymphoma, no infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy, no HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable, and no myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
1.1	Effective Date: 08/08/2024	Updated to include the new indication of relapsed or refractory follicular lymphoma and remove the requirement that the disease is CD20 positive
1.0	Effective Date: 08/21/2023	New Policy

Evenity® (romosozumab-aqqg)
HCPCS: J3111

Background Information:

- Evenity is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, 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.

- Approximately 54 million people in the United States have osteoporosis or another form of low bone mass. Breakdown of bone structure may be the result of natural aging and calcium deficiency (e.g., senile osteoporosis) or due to hormonal changes as in post-menopause. The decrease in bone mass and deterioration of bone tissue in osteoporosis can result in bone fragility and potential for fractures. Fractures related to osteoporosis and bone loss are a concern because of the high morbidity and mortality rate and economic burden. The National Osteoporosis Foundation estimates that 1 in 2 women and 1 in 4 men over 50 years of age will break a bone as a result of osteoporosis, resulting in $19 billion in related costs every 2 years and 2 million broken bones.

- The American Association for Clinical Endocrinology (AACE)/American College of Endocrinology (ACE) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis (2020) consider a diagnosis of osteoporosis and recommend pharmacologic therapy for the following clinical scenarios:

    - Presence or history of fragility fractures in the absence of other metabolic bone disorders, even in those with normal bone mineral density (BMD) as measured by axial dual-energy X-ray absorptiometry (DXA) scan

    - T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, or 1/3 radius; measured by DXA scan

    - T-score between -1.0 and -2.5 and if the FRAX® (fracture risk assessment tool) 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% in the United States or above the country-specific threshold in other countries or regions

        - The FRAX® tool (www.shef.ac.uk/FRAX) was developed by the World Health Organization (WHO) to evaluate fracture risk of patients. It integrates clinical risk factors with BMD at the femoral neck. The FRAX® tool provides the 10-year probability of fracture. The output is a 10-year probability of hip fracture and a 10-year probability of major osteoporotic fracture (forearm, shoulder, or clinical vertebral fracture).

- AACE/ACE guidelines separate patients with osteoporosis into two categories – high risk or very high risk. Patients who have had a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than − 3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (e.g., major osteoporosis fracture > 30%, hip fracture > 4.5%) or other validated fracture risk algorithm should be considered to be at very high fracture risk. All other patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, are considered to be high risk.

- The Endocrine Society 2020 Guidelines for the Pharmacological Management of Osteoporosis in Postmenopausal Women separate patients into 4 categories. Their high risk and very high risk categories align with those defined by the AACE/ACE guidelines. However, they also identify patients as low risk if they have no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, a 10-year hip fracture risk < 3%, and 10-year risk of major osteoporotic fractures < 20% or moderate risk when they have no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, and 10-year hip fracture risk < 3% or risk of major osteoporotic fractures < 20%.

- AACE/ACE guidelines recommend bisphosphonates (alendronate, risedronate, IV zoledronate) and Prolia (denosumab) the initial treatment option for patients with high-risk osteoporosis without prior fracture. Bisphosphonates decrease the breakdown of the bone (antiresorptive) and have been shown to increase BMD and reduce the incidence of fractures in patients with osteoporosis. Contraindications to bisphosphonates include hypocalcemia and severe renal impairment. In addition, oral bisphosphonates are contraindicated in patients with the inability to stand or sit upright for at least 30 minutes and may not be an appropriate option in patients with underlying gastrointestinal issues. However, use of an IV bisphosphonate is still appropriate in these situations. Prolia (denosumab) is another antiresorptive therapy that prevents the interaction of receptor activator of nuclear factor-kB ligand (RANKL) with its receptor on osteoclasts and osteoclast precursors and reversibly inhibits osteoclast-mediated bone resorption.

- AACE/ACE guidelines include evidence supporting superiority of certain antiresorptive agents (Prolia and IV zoledronate) and anabolic agents (Evenity, Tymlos®, and Forteo®) over oral bisphosphonates for individuals who are unable to use oral bisphosphonates and as initial therapy or for individuals with osteoporosis who are at very high risk for fracture. These guidelines do not give preference to one therapy over another.

- The Endocrine Society guidelines recommend initial treatment of patients at moderate risk with bisphosphonates (oral or IV) as initial therapy. For patients in the high to very high risk categories, the treatment algorithm recommends bisphosphonates, denosumab, teriparatide, abaloparatide, or romosuzumab all with adjunct calcium and vitamin D therapy as their treatment options.

- Guidelines recommend sequential treatment with antiresorptive osteoporosis therapies to maintain BMD gains and reduce fracture risk after completing a course of treatment with anabolic drugs.

- Until the effect of combination therapy on fracture risk is better understood, the AACE does not recommend concomitant use of FDA approved osteoporosis agents for the prevention or treatment of postmenopausal osteoporosis.

- Guidelines also do not recommend use of one anabolic agent over another as there is insufficient evidence to establish one as safer or more effective than another.

- The goal of monitoring osteoporosis is to identify those who have significant bone loss. AACE recommends repeat DXA scan every 1 to 2 years after initiation of therapy until BMD is stable. Bone turnover markers (BTMs) are also useful for assessing patient compliance and efficacy of therapy. Reductions in BTMs are conferred by antiresorptive therapy and are associated with fracture reduction. Significant increases in BTMs indicate good response to anabolic therapy.

- Evenity is limited to a 12 month duration of treatment. After 12 monthly doses, the anabolic effect of Evenity wanes, which is the reason for the duration limit. If osteoporosis therapy is still necessary, continued treatment with an antiresorptive agent should be considered (e.g., a bisphosphonate).

References:

1. Forteo [prescribing information]. Indianapolis, IN: Eli Lilly; July 2024.
2. Teriparatide [prescribing information]. Morristown, NJ: Alvogen; November 2023.
3. Tymlos [prescribing information]. Waltham, MA: Radius Health; December 2023.
4. Evenity [package insert]. Thousand Oaks, CA: Amgen; April 2020.
5. Bisphosphonates. Facts and Comparisons. 2020. Available from Wolters Kluwer Health, Inc.
6. Humphrey, M, Russell L, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care & Research. 2023;2088-2102.
7. Shoback D, Rosen C, Black D et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update, The Journal of Clinical Endocrinology & Metabolism, Volume 105, Issue 3, March 2020, dgaa048, https://doi.org/10.1210/clinem/dgaa048.
8. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis-2020 Update. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2020;26:1-46.
9. Prolia [prescribing information]. Thousand Oaks, CA: Amgen; March 2024.

Policy History		
#	Date	Change Description
1.5	Effective Date: 05/27/2025 P&T Date: 04/10/2025	Updated to define osteoporosis, add step for patients who are high-risk thru a bisphosphonate and Prolia, add a step for patients who are very high risk thru zoledronate or denosumab product if zoledronate is contraindicated and defined very high risk, and removed specific timeline for trial of bisphosphonates
1.4	Effective Date: 04/11/2024	Annual review - no changes made to existing criteria
1.3	Effective Date: 04/06/2023	Annual review – No changes made to existing criteria
1.2	Effective Date: 04/14/2022	Updated to allow for clinical situations where patients are not required to use bisphosphonates as first line treatment
1.1	Effective Date: 10/07/2021	Annual review of criteria was performed, no changes were made.
1.0	Effective Date: 01/01/2021	New Policy

Evkeeza™ (evinacumab-dgnb)
HCPCS: J1305

Background Information:

- Homozygous familial hypercholesterolemia (HoFH) is an ultra-rare inherited disease affecting approximately 1,300 patients in the United States. Patients with HoFH have mutations in the LDL receptor that result in virtually absent or impaired receptor-mediated catabolism of LDL cholesterol (LDL-C), leading to severely elevated LDL-C levels (> 400 mg/dL) and a lack of responsiveness to standard lipid-lowering therapies. Persistently elevated LDL-C increases the risk of premature atherosclerotic cardiovascular disease (ASCVD) and cardiac events in HoFH patients, often manifesting as early as the teenage years.

- HoFH can be diagnosed via genetic testing for causative mutations in the *LDLR*, *APOB*, and *PCSK9* genes, with *LDLR* mutations being the most common. Clinical diagnosis of HoFH can also be made in patients with an untreated LDL-C > 500 mg/dL or treated LDL-C ≥ 300 mg/dL, plus one of the following: cutaneous or tendon xanthoma prior to 10 years of age, or elevated LDL-C levels in both parents consistent with heterozygous familial hypercholesterolemia (HeFH). Of note, untreated LDL-C < 500 mg/dL may be present in some patients with HoFH; this may particularly be the case in young children and would warrant consideration of genetic testing to confirm or clarify the diagnosis.

- In their 2018 guideline on the management of blood cholesterol, the American College of Cardiology (ACC) and American Heart Association (AHA) task force on clinical practice guidelines recommends treatment with high intensity or maximally tolerated statin therapy for adult patients with LDL-C levels ≥ 190 mg/dL due to the increased risk of atherosclerotic cardiovascular disease (ASCVD) and both premature and recurrent coronary events. High intensity statins (atorvastatin 40 mg – 80 mg and rosuvastatin 20 mg – 40 mg) are expected to lower LDL-C by at least 50% and in clinical trials have been shown to provide greater ASCVD risk reduction than moderate intensity statins or placebo.

- If with a high-intensity statin the patient experiences statin-associated side effects that are not severe (e.g., myalgias), the statin dose can be reduced or alternate statins can be trialed with the ultimate goal of treating with a guideline-recommended maximally tolerated statin. There are a variety of generically available statins that can be dosed at different intensities or dosing regimens to help mitigate bothersome side effects; therefore, it is reasonable to require a trial of at least two statins in patients experiencing statin-associated side effects. Patients who experience more severe side effects with statin therapy (e.g. rhabdomyolysis) or recurrent statin-associated muscle symptoms despite multiple statin rechallenge attempts may need to discontinue statin use and transition to non-statin therapy that has been shown to provide clinical benefit.

- If maximally tolerated statin therapy fails to reduce LDL-C by at least 50% and/or the LDL-C level remains ≥ 100 mg/dL, the 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-C lowering recommends considering adding either ezetimibe or a PCSK9 monoclonal antibody as the initial non-statin therapy. Preference of which agent to add may be influenced by the desired amount of

LDL-C-lowering. ACC/AHA guidelines suggest that additional ASCVD risk reduction can be derived by adding ezetimibe to statin therapy, which can lower LDL-C by an additional 13-20%, and placebo-controlled randomized clinical trials have demonstrated favorable safety profiles and additional LDL-C reduction ranging from 43-64% with PCSK9 inhibitors in patients on maximally tolerated statin therapy. The available PCSK9 inhibitors include Repatha® (evolocumab), Praluent® (alirocumab), and Leqvio® (inclisiran). Of these, only Repatha and Praluent have approved indications as adjuncts to other LDL-C lowering therapies for the treatment of HoFH.

- If patients with HoFH have had an inadequate response to statins with or without ezetimine and PCSK9 inhibitors, specialized therapies like Evkeeza, lomitapide, or LDL apheresis may be needed to control LDL-C and, per the 2022 ACC guidance, are best administered under care of a lipid specialist.

- For children and adolescents 10 years of age and older with an LDL-C $\geq$ 190 mg/dL or $\geq$ 160 mg/dL with a clinical presentation consistent with familial hypercholesterolemia who do not respond adequately to 3 to 6 months of lifestyle therapy, the 2018 guidelines suggest initiation of statin therapy. Statin treatment intensity in children is not specified in the guidelines as it should be individualized to the child based on the severity of hypercholesterolemia and the needs of the child/family.

- Use of non-statin therapies to further treat HoFH in children is not addressed in the guidelines; however, since Repatha is approved by the FDA for use in pediatric patients 10 years of age and older with HoFH in combination with diet and other LDL-C lowering therapies, it is a reasonable next step for children and adolescents who require additional LDL-C lowering. Praluent, however, is only approved for adult patients with HoFH.

- Evkeeza (evinacumab-dgnb) is a novel therapy for the treatment of HoFH, approved as an adjunct to other LDL-C-lowering therapies for both adults and pediatric patients 5 years of age and older. It is the first FDA-approved treatment that binds to and blocks angiopoietin-like 3 (ANGPTL3), a protein that aids in lipid metabolism. Due to the mutations affecting LDL receptor function, patients with HoFH are often less responsive or unresponsive to standard lipid-lowering therapies (e.g. statins, PCSK9 inhibitors) whose mechanism of action largely depend on up-regulating LDL receptor function. By inhibiting ANGPTL3, Evkeeza is able to significantly reduce LDL-C levels independent of LDL receptor function.

- The Phase III ELIPSE HoFH trial demonstrated that Evkeeza, when taken in addition to other lipid-lowering therapies (including maximally tolerated statins, PCSK9 inhibitors, ezetimibe, lomitapide, and LDL apheresis), reduced LDL-C by a statistically significant 49% after 24 weeks compared to a 2% increase with lipid-lowering therapies alone (placebo) in patients with HoFH. Similar LDL-C lowering effects were observed in even the most difficult-to-treat patients who were unresponsive to other therapies due to limited or absent LDL receptor function.

- Of note, the safety and efficacy of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH). Additionally, the effects of Evkeeza on cardiovascular morbidity and mortality have not yet

been determined; however, it has been established that lowering LDL-C confers a lowered cardiovascular risk that is proportional to the reduction in LDL-C levels.

References:

1. Evkeeza [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc; March 2023.
2. Repatha [prescribing information]. Thousand Oaks, CA: Amgen Inc; August 2022.
3. Praluent [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc.; April 2021.
4. Bouhairie VE and Goldberg AC. Familial Hypercholesterolemia. Cardiol Clin. 2015 May; 33(2): 169-179. doi: 10.1016/j.ccl.2015.01.001.
5. Raal FJ et al. Evinacumab for Homozygous Familial Hypercholesterolemia. N Engl J Med 2020; 383: 711-20.
6. Raal FJ et al. Familial hypercholesterolemia treatments: Guidelines and new therapies. Atherosclerosis 277 (2018) 483-492.
7. Lloyd-Jones et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. JACC Vol. 70. No. 14. 2017: 1785-822.
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10. Rosenson RS and Durrington P. Familial hypercholesterolemia in adults: Overview. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
11. Rosenson RS and Durrington P. Familial hypercholesterolemia in adults: Treatment. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
12. Lloyd-Jones D, Morris P, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. J Am Coll Cardiol. 2022 Oct, 80 (14) 1366–1418.

Policy History		
#	Date	Change Description
1.5	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/09/2022	Removed criteria requiring trial and failure of a preferred PCSK9 inhibitor; will leverage trial and failure of preferred criteria (bullet f) instead for flexibility
1.1	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made.

1.0	Effective Date: 11/01/2021	New Policy

Exdensur (depemokimab-ulaa)
HCPCS: J3590

Background Information:

- Exdensur is indicated for add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older.

    - Limitations of Use: Not for relief of acute bronchospasm or status asthmaticus.

- Severe asthma is defined as asthma that requires treatment with medium- to high-dose inhaled corticosteroids plus a second therapy (i.e., systemic corticosteroid or biologic) to prevent it from becoming uncontrolled, or which remains uncontrolled despite therapy. Type 2 inflammation is the underlying cause of pathology in more than 80% of patients with severe asthma, in which patients exhibit elevated levels of eosinophils. Around 4-10% of the 25+ million Americans with asthma have severe asthma with a suggestion that around 700,000 U.S. individuals would be eligible for a biologic, though actual use is lower.

- The 2025 Global Strategy for Asthma Management and Prevention (GINA guidelines 2025), which has not been updated to include Exdensur at this time, recommends add-on biologic therapy for patients with uncontrolled severe asthma despite optimized maximal therapy and includes:

    - Add-on anti-immunoglobulin E (anti-IgE) (subcutaneous (SC) omalizumab) treatment: for patients aged ≥6 years with severe allergic asthma (Evidence A).

    - Add-on anti-IL-5/5R treatment (SC mepolizumab for patients aged ≥6 years; intravenous (IV) reslizumab for ages ≥18 years; or SC benralizumab for ages ≥12 years), with severe eosinophilic asthma (Evidence A).

    - Add-on anti-IL-4Rα treatment (SC dupilumab) for patients aged ≥6 years with severe eosinophilic/Type 2 asthma, or those requiring treatment with maintenance OCS (Evidence A).

    - Add-on anti-thymic stromal lymphopoietin (anti-TSLP) (SC tezepelumab): for patients aged ≥12 years with severe asthma (Evidence A).

- The efficacy of Exdensur for the add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype was evaluated in 2 replicate, randomized (2:1 to Exdensur or placebo), double-blind, parallel-group, placebo-controlled, multicenter clinical trials (SWIFT-1 and SWIFT-2) of 52 weeks duration. The trials enrolled adult and pediatric patients aged 12 years and older with asthma characterized by an eosinophilic phenotype, defined as a blood eosinophil count ≥150 cells/mcL at screening or ≥300 cells/mcL documented in the year prior to study entry. Patients were required to have 2 or more asthma exacerbations requiring treatment with systemic corticosteroids (SCS) in the prior

year while on background asthma therapy consisting of a medium- to high-dose inhaled corticosteroids (ICS) plus at least one additional asthma controller with or without maintenance oral corticosteroids (OCS).

- In these studies, Exdensur demonstrated sustained exacerbation reduction with two doses per year versus placebo, both plus standard of care. Treatment with Exdensur resulted in a significant 58% and 48% reduction in the rate of annualized asthma exacerbations (AER; asthma attacks) over 52 weeks from SWIFT-1 and SWIFT-2, respectively (p-value: SWIFT-1 $p<0.001$ and SWIFT-2 $p<0.001$).

- In a secondary endpoint from SWIFT-1 and SWIFT-2, patients treated with Exdensur experienced numerically fewer exacerbations requiring hospitalization and/or emergency department (ED) visits (1% and 4%) compared with placebo (8% and 10%), respectively.

    - A pre-specified pooled analysis of the two trials showed there was a 72% reduction in the annualized rate of clinically significant exacerbations requiring hospitalization and/or ED visits over 52 weeks for Exdensur compared with placebo (p=0.002).

- Across these trials, Exdensur was well-tolerated, with patients experiencing a similar rate and severity of side effects as those receiving placebo.

References:

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Policy History		
#	Date	Change Description
1.0	Effective Date: 02/12/2026	New Policy

Fasenra™ (benralizumab)
HCPCS: J0517

Background Information:

- Fasenra is the third interleukin-5 (IL-5) receptor antagonist indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Fasenra is also indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

- Eosinophilic asthma is a sub phenotype of severe asthma characterized by elevated sputum and blood eosinophil levels as well as increased asthma severity, atopy, late-onset disease, and steroid refractoriness.

- Severe asthma requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite therapy. Add-on treatment for severe asthma include LAMA, leukotriene receptor antagonist (LTRA), low dose azithromycin (adults) and biologic agents for severe allergic or severe type 2 asthma. Type 2 inflammation is found in the majority of people with severe asthma and is characterized by production of cytokines such as interleukin. Anti-IL5 monoclonal antibodies (Cinqair®, Nucala®, and Fasenra) specifically target formation of eosinophils and depletes blood eosinophil levels.

- The Global Institute for Asthma (GINA) 2023 Difficult-to-Treat & Severe Asthma Diagnosis and Management guidelines recommend those with severe asthma and Type 2 airway inflammation (blood eosinophils ≥ 150/μL and/or fractional exhaled nitric oxide (FeNO) ≥20 ppb and/or sputum eosinophils ≥2%, and/or asthma is clinically allergen driven) first should consider adherence tests and consider increasing the ICS dose for 3-6 months. Add-on Type 2-targeted biologic therapy should be considered for patients with exacerbations or poor symptom control on high dose ICS-LABA. Local payer eligibility criteria and comorbidities should also be considered. Anti-IL5/anti-IL5R, including Fasenra, is appropriate in patients with exacerbations in the last year and blood eosinophils ≥ 150/μL.

- A peripheral blood eosinophil count is an indirect way to estimate airway inflammation. A blood eosinophil count ≥ 300 cells/microliter may help to predict asthmatics who are at increased risk for exacerbations in the next year. Furthermore, a count-response relation exists between blood eosinophil counts and asthma-related outcomes. The European Respiratory Society/American Thoracic Society guidelines from 2020 suggest that treatment of severe asthma be guided by clinical criteria and biomarkers such as blood eosinophil levels or FeNO, rather than by clinical criteria alone. In addition, it also suggests that a blood eosinophil count cut-off point of ≥ 150 cells/microliter can be used to guide anti-IL5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations.

- Approval was based on results from a total of 3 multicenter, randomized, double-blind trials.

- Two asthma exacerbation trials, SIROCCO (n = 1,204) and CALIMA (n = 1,306), randomized patients 12 to 75 years old with severe asthma not controlled on high dose (medium – high in CALIMA) ICS/LABA therapy to receive Fasenra 30 mg every 4 weeks, Fasenra 30 mg every 8 weeks, and placebo. The addition of Fasenra 30 mg SC every 8 weeks to current therapy significantly reduced asthma exacerbation rates by 51% in SIROCCO and 28% in CALIMA in patients with baseline blood eosinophil levels ≥ 300 cells/microliter.

- The oral corticosteroid (OCS) reduction study (ZONDA) included 220 patients aged 18 years and older with severe asthma receiving high-dose ICS/LABA and chronic OCS with a baseline blood eosinophil level of ≥ 150 cells/microliter. Significantly more patients receiving Fasenra 30 mg SC every 8 weeks were able to reduce their OCS dose compared to placebo. Patients using Fasenra saw 75% reduction in median daily OCS vs. 25% in the placebo group.

- Review response to biologic therapy after 3-4 months of treatment. If the patient had a good response, the need for each medication should re-evaluated, but do not completely stop inhaled therapy. Consider gradually decreasing or stopping oral steroids first.

- Clinical reasons a patient may be unable to self-administer Fasenra include:

    - Patient or caregivers are unable to perform subcutaneous injections with proper technique

    - Member requires monthly medical support from the physician

- EGPA, formerly known as Churg-Strauss Syndrome, is a rare, immune-mediated inflammatory disease that is caused by inflammation of small to medium-sized blood vessels. It is estimated that 118,000 people throughout the world live with EGPA and approximately 15,000 patients living in the US have EGPA. EGPA can result in damage to multiple organs, including lungs, upper airway, skin, heart, gastrointestinal tract and nerves. The most common symptoms and signs include extreme fatigue, weight loss, muscle and joint pain, rashes, nerve pain, sinus and nasal symptoms, and shortness of breath. Without treatment, the disease may be fatal. Almost half (47%) of patients do not achieve remission with current treatments.

- There are limited treatment options for EGPA. Patients are often treated with chronic high-dose OCS and experience recurrent relapses when attempting to taper off OCS. Nucala is also approved for EGPA.

- Antineutrophil cytoplasmic antibodies (ANCAs) are found in 40%-60% of patients, but it is unknown whether ANCAs have a pathogenic role or if this is simply a manifestation of EGPA. EGPA is a multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia. It primarily affects the lungs, followed by the skin, but also involves the cardiovascular, gastrointestinal, renal, and central nervous systems. Asthma is the cardinal feature of EGPA, which presents, along with allergic rhinitis and nasal polyps, long before vasculitis and the initial EGPA diagnosis. The next phase of the disease is typically eosinophilia, high levels of eosinophils in the blood, which are 5% or

less in healthy patients and at least 10% and up to as high as 60% in EGPA patients. Vasculitis is the third and final phase of symptoms and includes several organs: fever, fatigue, sudden weight loss, muscle and joint pain, rash, numbness/tingling/loss of strength of hands or feet, chest pain or palpitations, shortness of breath, chronic cough, venous thrombotic events, abdominal pain, and blood in stool.

- Fasenra for EGPA was based on the MANDARA trial which was a Phase III, randomized, double-blinded, active-controlled trial that compared the efficacy and safety of Fasenra to mepolizumab in adult patients with relapsing or refractory EGPA. In the trial, 140 patients were randomized 1:1 to receive either a single 30 mg subcutaneous injection of Fasenra or three separate 100 mg subcutaneous injections of the active comparator every four weeks.

- EGPA diagnosis was based on history or presence asthma and eosinophilia (>1.0x10^9/L and/or >10% of leucocytes) and at least 2 of the following: biopsy with eosinophilic vasculitis or perivascular/granulomatous inflammation; mono-or polyneuropathy, non-fixed pulmonary infiltrates, sino-nasal abnormality; cardiomyopathy; glomerulonephritis; alveolar haemorrhage; palpable purpura; anti neutrophil cytoplasmic anti-body (ANCA) positivity (Myeloperoxidase or proteinease 3).

- The primary endpoint was the proportion of patients who were in remission at both weeks 36 and 48. Remission is defined as Birmingham Vasculitis Activity Score (BVAS)=0 and OCS dose less than or equal to 4 mg/day. A secondary endpoint was the proportion of patients who were able to fully taper off OCS at weeks 48 through 52. The primary statistical analysis was to demonstrate non-inferiority of Fasenra versus mepolizumab based on the primary endpoint.

- In the trial, nearly 60% of Fasenra-treated patients achieved remission which was comparable to mepolizumab-treated patients. Data also showed 41% of Fasenra-treated patients fully tapered off OCS (vs. 26% in the mepolizumab arm (difference: 16%; 95% CI: 1,31)).

References:

1. Fasenra [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; September 2024.
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5. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020; 55.

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Table 1: Comparative cumulative daily dosing of inhaled corticosteroids (mcg/day)

Inhaled Corticosteroid	Ages 12 and up			Ages 6-11		
	Low Dose	**Medium Dose**	**High Dose**	**Low Dose**	**Medium Dose**	**High Dose**
Beclometasone dipropionate HFA	100 – 200	>200 – 400	>400	50 – 100	>100 – 200	>200
Budesonide DPI	200 – 400	>400 – 800	>800	100 – 200	>200 – 400	>400
Budesonide nebules	NA	NA	NA	250 – 500	>500 – 1,000	>1,000
Ciclesonide HFA	80 – 160	>160 – 320	>320	80	>80 – 160	>160
Fluticasone furoate DPI	100	NA	200	NA	NA	NA
Fluticasone propionate DPI	100 – 250	>250 – 500	>500	100 – 200	>200 – 400	>400
Fluticasone propionate HFA	100 – 250	>250 – 500	>500	100 – 200	>200 – 500	>500
Mometasone furoate	110 – 220	>220 – 440	>440	110	≥220 - <440	≥440
Triamcinolone acetonide	400 – 1,000	>1,000 – 2,000	>2,000	400 – 800	>800 – 1,200	>1,200

Policy History		
#	Date	Change Description
1.7	Effective Date: 12/04/2025	Annual review of policy; no changes were made to the criteria

1.6	Effective Date: 12/12/2024	Updated to include newly approved indication for eosinophilic granulomatosis with polyangiitis.
1.5	Effective Date: 10/03/2024	Replaced the “not to be used in combination with other biologics statement for the treatment of asthma” to “not to be used in combination with other biologics or targeted DMARDs for the same indication” to align with other biologic policies
1.4	Effective Date: 10/12/2023	Annual review of policy; no changes were made to the criteria.
1.3	Effective Date: 10/06/2022	Updated to require self-administration unless clinically unable to do so
1.2	Effective Date: 10/07/2021	Updated LABA and LAMA requirement to LABA or LAMA
1.1	Effective Date: 06/10/2021	Criteria document created and criteria aligned between all biologic asthma agents. The criteria for asthma was previously part of the Biologics for Asthma Policy which will be retired
1.0	Effective Date: 01/01/2021	New Policy

General Drug Utilization Management Policy
FDA Approved Drugs
Unapproved Drugs
Not Otherwise Classified (NOC) Drugs

Background Information:

The purpose of this policy is to provide:

- Allow management of any drug according to the prescribing information.
- Immediate criteria for new FDA approved drugs. This policy will represent drugs which are pending a full or abbreviated drug review for the P&T Committee.
- Immediate criteria for existing drugs which have received a new FDA approved indication for which the medical policy has yet not been updated with this most recent indication. The new FDA approved indication will be represented by this policy until it is reviewed by the P&T Committee.
- Immediate criteria for all drugs where we will follow up with development of a full drug/class specific policy if the criteria are more restrictive than the prescribing information.
- When available, the applicable complete drug review with full criteria or policy will take precedence over this policy.
- Allows Medicare Part D to apply general management as listed according to CMS guidance

Policy History		
#	Date	Change Description
1.3	Effective Date: 12/04/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 12/12/2024	Updated to add alternative authorization period for drugs managed to label under General UM Policy by oncology vendor.
1.1	Effective Date: 06/06/2024	Updated policy to remove criteria related to investigational drugs and updated authorization period to align with PA60.
1.0	Effective Date: 06/08/2023	New Policy

Givlaari® (givosiran)
HCPCS: J0223

Background Information:

- Acute Hepatic Porphyria (AHP) is a rare, autosomal dominant disorder with 4 different variations (Acute Intermittent Porphyria, Hereditary Coproporphyria, Variegate Porphyria, and ALA Dehydratase-Deficient Porphyria) that results from a partial deficiency in 4 enzymes that are part of the heme biosynthetic pathway leading to an accumulation of toxic heme intermediaries, aminolevulinic acid (ALA) and porphobilinogen (PBG), which are thought to cause the clinical manifestations of AHP.

- An estimated 5,000 patients in the US and Europe suffer from AHP attacks annually, and 500 to 1,000 experience recurrent attacks. The incidence and prevalence of AHP in Sweden is 4 times as high compared to the rest of Europe.

- Signs and symptoms of AHP are generally nonspecific and typically occur as intermittent acute attacks that are sometimes life-threatening. The most common symptoms include abdominal pain, vomiting, constipation, muscle weakness, psychiatric symptoms, hypertension, painful urination, and urinary retention or incontinence. Acute attacks are usually associated with exacerbating factors, such as medications, smoking, sex hormones, fasting and stress.

- Most patients have a complete resolution in their symptoms between attacks; however, some patients develop chronic symptoms including pain requiring opioid analgesics, depression/anxiety, and persistent hypertension.

- The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network (2017) guidelines provide the following recommendations for long-term management of AHP:

    - Management should focus on the identification and avoidance of factors that precipitate or worsen acute AHP attacks. Patients should be counseled to avoid certain environmental triggers, including certain medications, crash dieting or fasting-type dieting, smoking (tobacco and marijuana), and alcohol. Patients should be counseled to consult publicly available drug database such as http://www.drugs-prophyria.org before starting new medications.

    - Prophylactic therapy with hemin or intravenous glucose can decrease ALAS-1 activity after 2-3 infusions, with hemin having a more potent effect. Hemin is often used for more severe attacks while glucose loading is used for only mild attacks with improvement in symptoms generally seen within 3-4 days. Patients who experience four or more attacks per year may require hemin prophylaxis up to twice weekly; however, some patients do report improvement with monthly infusions.

    - Severe iron overload can occur with recurrent heme administration leading to the necessity of therapeutic phlebotomy when ferritin levels are >1000 ng/mL.

    - Supportive therapy to address symptoms of AHP may be needed, including pain medications (such as opioids), electrolyte replacement, anticonvulsants, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and calcium channel blockers.

    - Liver transplantation is a last-line option for AHP which has been shown to be curative; however, due to significant morbidity and mortality associated with liver transplantation, this surgical procedure is reserved for those with severe, disabling, intractable attacks that are refractory to hemin therapy.

    - Clinical trials assessing Givlaari as treatment in AHP were ongoing at the time of publication of the Porphyria Consortium's guidelines (2017); therefore, current guidelines do not include recommendations for Givlaari in the setting of AHP.

- The American Gastroenterological Association (AGA) Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review (2023) provides additional recommendations regarding the diagnosis and management of AHP including the following Best Practice Statements:

    - Initial diagnosis of AHP should be made by biochemical testing measuring ALA, PBG, porphyrins, and creatinine in a random urine sample.

    - Genetic testing should be used to confirm the diagnosis of AHP in patients with positive biochemical testing.

    - Prophylactic heme therapy or givosiran, administered in an outpatient setting, should be considered in patients with recurrent attacks (4 or more per year).

- Givlaari (givosiran) is the first and only FDA-approved therapy for the treatment of adults with AHP. Givlaari is a double-stranded small interfering RNA (siRNA) which acts in the liver to reduce circulating levels of neurotoxic intermediaries, ALA and PBG.

- Givlaari was evaluated in a Phase III, double-blind, placebo-controlled trial (ENVISION, NCT03338816), which enrolled 94 patients ages 12 years of age and older with symptomatic AHP and at least 2 documented porphyria attacks within the last 6 months. Of the 94 patients enrolled in the trial, 89 had Acute Intermittent Porphyria, 1 had Hereditary Coproporphyria, 2 had Variegate Porphyria, and 2 had Acute Hepatic Porphyria without an identified mutation.

- Methods: Patients were randomized to receive once monthly injections of either subcutaneous Givlaari at a dose of 2.5 mg/kg (N=48) or placebo (N=46) for a total of 6 months.

- Endpoints: The primary endpoint was reduction relative to placebo in the annualized rate of composite porphyria attacks among patients with acute intermittent porphyria (the most common subtype of AHP), defined as attacks requiring hospitalization, an urgent healthcare visit, or hemin administration. Key secondary endpoints included evaluation of ALA and PGP levels in addition to hemin use in patients with Acute Intermittent Porphyria.

- Results:

    - Primary endpoint: In patients with Acute Intermittent Porphyria, the average annualized rate of composite porphyria attacks over 6 months was 3.2 (95% CI: 2.3 – 4.6) in the Givlaari group compared to 12.5 (95% CI: 9.4 – 16.8) in the placebo group, representing a 74% lower rate of averaged annualized attacks for the Givlaari group ($p<0.001$). Results were similar for patients with other subtypes of AHP.

- Secondary endpoints: Among patients with Acute Intermittent Porphyria, treatment with Givlaari led to significantly lower levels of urinary ALA and PGP and fewer days of hemin use (6.8 days v. 29.7 days) compared to the placebo.

References:

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Policy History		
#	Date	Change Description
1.3	Effective Date: 02/12/2026	Annual review no changes to criteria
1.2	Effective Date: 02/13/2025	Annual review no changes to criteria
1.1	Effective Date: 02/08/2024	Updated to remove the specialist prescriber requirement and change the renewal criteria to standard language
1.0	Effective Date: 05/01/2023	New Policy

Hemgenix® (etranacogene dezaparvovec-drlb)
HCPCS: J1411

Background Information:

- Hemgenix is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with hemophilia B who currently use factor IX prophylaxis therapy, or have a current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

- Hemophilia B is a rare genetic bleeding disorder in which affected individuals have insufficient levels of factor IX. It is the second most common type of hemophilia and caused by mutations in the F9 gene. The F9 gene is located on the X chromosome and thus the disease is inherited as an X-linked recessive trait. About 30% of cases are the result of spontaneous genetic mutations. Studies report that over 50% of people newly diagnosed with severe hemophilia have no prior family history. Overall incidence is estimated at 1 in 25,000 male births.

- The symptoms and severity of hemophilia B may vary greatly from one person to another. Hemophilia B can range from mild to moderate to severe.

- Mild hemophilia patients have a factor activity of 5% to 40% and usually do not experience any major problems in everyday life. It often goes unnoticed until puberty or adulthood when bleeding after surgery or a deep cut lasts longer than normal. These patients do not typically need prophylactic therapy and only require on-demand factor for injuries or surgeries.

- Moderate hemophilia patients have a factor activity of 1% to 5% and may have occasional episodes of spontaneous bleeding from deep tissues such as joints and muscles. These episodes are usually associated with some injury or inciting event. Individuals with moderate hemophilia B are at risk for prolonged bleeding following surgery or trauma. Affected individuals are usually diagnosed by 5 or 6 years of age. The frequency of spontaneous bleeding episodes in individuals with moderate hemophilia B is highly variable resulting in some patients needing consistent prophylactic factor IX and others only needing on-demand factor IX for medical procedures.

- Severe hemophilia patients have a factor level of less than 1% and often have bleeding for no known reason, especially in the joints and muscles. From infancy, patients bruise easily and as they become more active, learn to walk, and put more strain on their joints and muscles, bleeding starts to occur. Without preventative treatment, a young child may experience 2 to 5 spontaneous bleeding episodes per month.

- Hemophilia B should be suspected in individuals presenting with a history of easy bruising, spontaneous bleeding, particularly into the joints, muscles, and soft tissues, or excessive bleeding following trauma or surgery. If hemophilia is suspected, the clinician should obtain the patient's bleeding history and family history of abnormal or unexplained bleeding experienced by any siblings or maternal male relatives to

assess patterns of inheritance and assist with diagnosis. A definitive hemophilia B diagnosis is based on a factor assay to demonstrate a deficiency of factor IX. Once an individual is diagnosed with hemophilia B, the specific mutation in the F9 gene responsible for causing hemophilia may be identified.

- The current standard of care for hemophilia B is the use of factor IX replacement therapy. There are two types of factor products available to treat hemophilia which include plasma derived factor, entirely made of plasma from human donations and recombinant factor, which is made by genetically engineered technology, both with standard and extended half-life products. All factor products have demonstrated to have similar safety and efficacy in clinical studies treating or reducing bleeding episodes with the apparent difference in the frequency of administration: up to three times weekly injections for standard products and weekly or every two weeks for extended half-life products. To be enrolled in the HOPE-B trial, patients needed to be stable on factor IX therapy for 6 months prior Hemgenix administration.

- It is estimated that less than 5% of individuals with severe hemophilia B develop inhibitors against factor IX replacement therapy. Inhibitors most often develop during childhood, especially during the first 20 exposure days. Exposure days are counted as a day during which a patient receives factor. Controlling bleeds is a greater challenge in hemophilia patients with inhibitors than in those without. Inhibitors to factor IX are associated with a higher disease burden, including increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges, all of which may impact a patient's physical functioning, capacity for physical activities, and quality of life. The definition of a positive inhibitor is a Bethesda titer of greater than or equal to 0.3 BU for factor IX. Patients positive for factor IX inhibitors or with a prior history of factor IX inhibitors were excluded from the HOPE-B trial. In order to limit the risk of inhibitor development following Hemgenix therapy, the HOPE-B study also required patients had greater than 150 prior exposure days to factor IX therapy before receiving gene therapy.

- Hemgenix uses an adeno-associated virus serotype 5 vector (AAV5) to deliver a functional copy of the F9 gene to the patient's liver where functional factor IX is produced. Patients with high AAV5 antibody titers may not respond to gene therapy due to the antibodies neutralizing Hemgenix before the functional F9 gene can be properly incorporated into the patient's genome. The HOPE-B study did not exclude patients from the trial based on antibody titers, however, the trial had one non-responder to treatment whose antibody titer level was 1:700. It is important for physicians to be aware of the patients antibody titer levels before administering treatment.

- A provider portal is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

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Policy History		
#	Date	Change Description
1.4	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/08/2023	Removed confirmation of diagnosis via decreased factor IX levels
1.1	Effective Date: 02/02/2023	New policy
1.0	Initial Effective Date: 12/05/2022	New policy

Hemophilia Class Policy
HCPCS: See Appendix A below

Background Information:

- There are two types of hemophilia: hemophilia A and hemophilia B
    - Hemophilia A is defined as a deficiency in factor VIII clotting factor
    - Hemophilia B is defined as a deficiency in factor IX clotting factor

- There are three main levels of severity
    - Mild hemophilia patients have a factor activity of 5% to 40% and usually do not experience any major problems in everyday life. It often goes unnoticed until puberty or adulthood when bleeding after surgery or a deep cut lasts longer than normal. These patients do not typically need prophylactic therapy and only require on-demand factor for injuries or surgeries
    - Moderate hemophilia patients have a factor activity of 1% to 5% and may have occasional bleeding, but usually only following surgery or an injury. Only rarely will there be no apparent cause
    - Severe hemophilia patients have a factor level of less than 1% and often have bleeding for no known reason, especially in the joints and muscles. From infancy, patients bruise easily and as they become more active, learn to walk and put more strain on their joints and muscles, bleeding starts to occur

- Factor replacement therapy is the mainstay of treatment of prevention of bleeding episodes in hemophilia. There are two types of factor products available to treat hemophilia which include plasma derived factor, entirely made of plasma from human donations and recombinant factor, made by genetically engineered technology, both with standard and extended half-life products. There is also a highly sustained, extended half-life recombinant product. All factor products have demonstrated to have similar safety and efficacy in clinical studies treating or reducing bleeding episodes with the apparent difference in the frequency of administration: up to three times weekly injections for standard and weekly or twice weekly for extended half-life products.

- Despite widespread availability of safe and effective factor replacement therapy, patients with hemophilia continue to experience a tremendous burden of treatment, breakthrough bleeding, and progressive joint disease. Some of these issues may be addressed in select

patients with the use of non-factor therapies, such as, Hemlibra, Hympavzi, Alhemo, and Qfitlia. Hemlibra is a monoclonal immunoglobulin G4 (IgG4) antibody that bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis. It is indicated for use as prophylactic therapy for hemophilia A in patients with or without inhibitors. Hympavzi is a tissue factor pathway inhibitor (TFPI) antagonist that reduces the amount of tissue factor pathway inhibitor, thereby increasing the amount of thrombin generated. It is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and B without inhibitors. Alhemo is an additional TFPI indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and B with inhibitors. Qfitlia is an antithrombin-directed small interfering ribonucleic acid (siRNA) indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors

- Patients with severe hemophilia may develop an inhibitor sometime in their lives. Inhibitors most often develop during childhood, especially during the first 50 exposure days to factor replacement.

- Inhibitors are classified into two categories.

    - Those with a 5 or higher Bethesda units (BU)/mL result are classified as having a "high responding" inhibitor level.

    - Those who measure below 5 BU/mL are classified as having a "low responding" inhibitor level.

- Depending on the inhibitor level, different therapeutic options are available to patients.

    - Bypassing agents are used in the treatment of inhibitors. These contain factors that can stimulate the formation of a clot and stop bleeding. While these treatments are effective, many limitations exist including potential for bleeding or over-production of clots, and the need for frequent doses.

    - Hemlibra (emicizumab) is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX and factor X to restore the function of missing activated factor VIII in hemophilia A patients to restore hemostasis. Hemlibra has only been studied in patients with inhibitors greater than 5 BU/mL and has not been studied in combination with Immune Tolerance Induction therapy.

    - Alhemo (concizumab-mtci) is a TFPI that reduces the amount of tissue factor pathway inhibitor, thereby increasing the amount of thrombin generated resulting in a reduction in the number of bleeding episodes. Alhemo has only been studied in patients with inhibitors greater than 0.6 BU/mL and has not been studied in combination with Immune Tolerance Induction therapy. While Alhemo

has been studied in patients with 0.6 BU/mL inhibitors, those with inhibitors less than 5 BU/mL can be treated with higher doses of factor calculated to overcome the inhibitor titer and provide a hemostatic level.

- Qfitlia (fitusiran) is a siRNA that causes degradation of antithrombin (AT) messenger RNA (mRNA) through RNA interference, reducing plasma AT levels. Qfitlia has only been studied in patients with inhibitors greater than 0.6 BU/mL and has not been studied in combination with Immune Tolerance Induction therapy. While Qfitlia has been studied in patients with 0.6 BU/mL inhibitors, those with inhibitors less than 5 BU/mL can be treated with higher doses of factor calculated to overcome the inhibitor titer and provide a hemostatic level.

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Policy History		
#	Date	Change Description
1.7	Effective Date: 10/09/2025	Updated to allow use of Alhemo in patients without inhibitors in hemophilia A and hemophilia B
1.6	P&T Date: 06/05/2025 Effective Date: 07/21/2025	Updated to require a higher dose of factor in patients with inhibitors less than 5 BU/mL requesting Alhemo, require self-administration of all hemophilia products unless the member is clinically unable to do so, and include Qfitlia
1.5	Effective Date: 02/13/2025	Updated to include Alhemo
1.4	Effective Date: 12/12/2024	Updated to include Hympavzi and include the trial and failure of preferred products statement
1.3	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 04/06/2023	Updated to include Altuviiio
1.1	Effective Date: 04/22/2022	Updated to add wording only requiring antibody levels for Hemlibra when requesting doses above the FDA recommended regimen
1.0	Effective Date: 11/01/2021	New Policy

Appendix A

Medications covered by this policy include, but not limited to the following:

Medication Name	Benefit	HCPCS
Advate	Medical	J7192
Adynovate	Medical	J7207
Afstyla	Medical	J7210
Alhemo	Medical	J3590
Alphanate	Medical	J7186
AlphaNine SD	Medical	J7193
Alprolix	Medical	J7201
Altuviiio	Medical	J7214
BeneFIX	Medical	J7195
Coagadex	Medical	J7175
Corifact	Medical	J7180
Eloctate	Medical	J7205
Esperoct	Medical	J7204
Feiba	Medical	J7198
Hemlibra	Medical	J7170
Hemofil M	Medical	J7190
Humate-P	Medical	J7187
Hympavzi	Medical	J3590
Idelvion	Medical	J7202
Ixinity	Medical	J7213
Jivi	Medical	J7208
Koate	Medical	J7190
Kogenate FS	Medical	J7192
Kovaltry	Medical	J7211
Mononine	Medical	J7193
Novoeight	Medical	J7182
NovoSeven RT	Medical	J7189
Nuwiq	Medical	J7209

Profilnine	Medical	J7194
Qfitlia	Medical	J3590
Rebinyn	Medical	J7203
Recombinate	Medical	J7192
Rixubis	Medical	J7200
Sevenfact	Medical	J7212
Tretten	Medical	J7181
Vonvendi	Medical	J7179
Wilate	Medical	J7183
Xyntha	Medical	J7185

Hyaluronic Acid Intra-Articular Injections	
Durolane	J7318
Euflexxa	J7323
Gel-One	J7326
Gelsyn-3	J7328
GenVisc 850	J7320
Hyalgan	J7321
Hymovis	J7322
Monovisc	J7327
Orthovisc	J7324
Supartz, FX	J7321
Synojoynt	J7331
Synvisc	J7325
Synvisc–One	J7325
Triluron	J7332
TriVisc	J7329

Background Information:

- Osteoarthritis (OA) is a common degenerative condition affecting the knees. It is characterized by deterioration and loss of the articular cartilage, subchondral sclerosis and osteophyte formation, and is often accompanied by inflammation of the synovium. Currently, no curative therapy is available for osteoarthritis and thus the overall goals of management are to reduce pain and prevent disability.

- Hyaluronan, also known as hyaluronate, hyaluronic acid or viscosupplementation, is a naturally occurring macromolecule that is a major component of synovial fluid and is thought to contribute to its viscoelastic properties. To date, over ten hyaluronans have received FDA approval, each using the 515 device approval path, which is obtained simply by demonstrating that the product is similar to a previously approved device. Current literature and guideline recommendations do not support the use of one hyaluronic acid product over another.

- FDA approved hyaluronic acid agents are indicated for the treatment of pain in knee OA in patients 18 years of age and older who have failed nonpharmacologic treatment and simple analgesics or NSAIDs. Knee OA requires a comprehensive plan for management, including physical, psychological, and/or pharmacologic therapies. The approved use for hyaluronic acid products aligns with the treatment recommendations laid out in the most recent guidelines for management of knee OA.

- 2019 American College of Rheumatology (ACR)/Arthritis Foundation (AF) Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee:

  - The 2019 ACR/AF guidelines strongly recommend the use of exercise, self-management programs, weight loss, tai chi, and gait aids (i.e. tibiofemoral knee brace, cane) in nonpharmacologic management of knee OA. Heat and therapeutic cooling, cognitive behavioral therapy, kinesiotaping, and yoga are additional nonpharmacologic options conditionally recommended for managing knee OA.

  - With regard to pharmacologic approaches to treatment, the guidelines strongly recommend the use of topical NSAIDs, keeping with the principle that local therapies with minimal systemic exposure are preferable prior to systemic. Oral NSAIDs and intra-articular glucocorticoids are also strongly recommended, with NSAIDs being the initial oral treatment of choice for knee OA. Acetaminophen, duloxetine, and tramadol are conditionally recommended.

  - Intraarticular hyaluronic acid injections are conditionally recommended against in patients with knee OA due to a lack of data demonstrating consistent benefit without trial bias; however, in clinical practice the choice to use hyaluronic acid in patients with knee OA who have had an inadequate response to nonpharmacologic and pharmacologic therapies may be more favorable than offering no intervention.

- 2019 Osteoarthritis Research Society International (OARSI) Guidelines for the Non-surgical Management of Knee, Hip, and Polyarticular Osteoarthritis.

  - The 2019 OARSI guidelines strongly emphasize core treatments (i.e. arthritis education, land-based exercise programs, mind-body exercise, dietary management) for all patients prior to initiating therapy.

  - Pharmacologic and nonpharmacologic treatments with a high consensus recommendation include aquatic exercise, gait aids, topical NSAIDs, oral NSAIDs, and intraarticular corticosteroids. Treatment with intra-articular hyaluronic acid is a low consensus recommendation and is conditionally recommended after achieving an inadequate response to high consensus treatment options.

  - The use of acetaminophen for knee OA was conditionally not recommended, while the use of oral and transdermal opioids was strongly not recommended.

- The 2021 American Academy of Orthopaedic Surgeons (AAOS) Evidence-Based Clinical Practice Guideline for the Management of OA of the Knee (Non-Arthroplasty) does not recommend hyaluronic acid intraarticular injection(s) for routine use in the treatment of

symptomatic OA of the knee (moderate strength recommendation). Though clinical trial results evaluating benefit with HA treatment have been mixed, the gudelines acknowledge that some studies have demonstrated statistically significant improvement in OA symptoms with the use of HA. As such, the group agrees that viscosupplementation may represent a viable option for select patient groups, particularly those that failed other treatments when appropriately indicated.

- Of note, the above guideline recommendations apply to patients with knee OA and no contraindications to recommended therapies. The choice of treatment(s) should be individualized to the patient, evaluating for contraindications, comorbidities, disease severity, past medical/surgical history, and personal preferences.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/03/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 10/12/2023	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 06/01/2023	New Policy

Ilumya™ (tildrakizumab-asmn)
HCPCS: J3245

Background Information:

- Ilumya is a an interleukin-23 (IL-23) antagonist indicated for the treatment of moderate-to-severe psoriasis in adults who are candidates for systemic therapy or phototherapy. Per the prescribing information, Ilumya should only be administered by a healthcare provider.

- Psoriasis is a chronic, painful and life-altering immune-mediated disease which predominantly manifests with skin and joint involvement. Patients may also experience significant cardiovascular and psychological comorbidities. Approximately 2% of U.S. adults are affected by psoriasis (men and women equally), and it can occur at any age. Approximately 90% of psoriasis-affected patients have plaque psoriasis, which is characterized by well-defined round or oval plaques that vary in size and often coalesce. The severity of psoriasis is defined as: mild = less than 3% of body affected; moderate = 3-10% of body affected; and severe being more than 10% of the body affected.

- Per the 2020 Joint American Academy of Dermatology - National Psoriasis Foundation (AAD/NPF) guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures: topical corticosteroids provide a high efficacy and good safety option for patients with localized disease. They are generally recommended as first-line therapy. Choice of steroid potency may depend on severity, location, patient preference, and patient age, while the duration of treatment may vary with steroid potency, location and severity of disease often ranging from 2-12 weeks. Therapeutic regimens may include 2-4 weeks with a topical steroid applied twice daily, followed by a maintenance regimen where topical steroids are alternated with a steroid-sparing topical agent. Treatment with topical steroids for over 12 weeks is recommended under careful supervision by a physician.

- Per the 2019 Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with phototherapy: phototherapy serves as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications or simply seeking an adjunct to a failing regimen. Guidelines also state that the majority of patients with mild-to-moderate disease have adequate disease control with topical therapies and phototherapy alone.

- Per the Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with systemic nonbiologic therapies: many oral medications, including methotrexate, cyclosporine, and acitretin, have been used for decades to treat psoriasis, each with its own benefits and risks. Most work by targeting the immune system, whereas others, such as acitretin, work predominantly by decreasing keratinocyte hyperproliferation, thus restoring the normal epidermal differentiation. Both methotrexate and cyclosporine are category A guideline recommendations for the treatment of moderate to severe psoriasis in adults and for severe, recalcitrant psoriasis, respectively. Studies

examining the use of methotrexate and cyclosporine in psoriasis showed the primary efficacy endpoints met within 12-16 weeks. Acitretin is a category B guideline recommendation as monotherapy for plaque psoriasis, with full treatment response expected within 3-6 months.

- Per the 2019 Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with biologics: biologic agents, as monotherapy or combined with other topical or systemic medications, have a high benefit-to-risk ration. Tumor necrosis factor (TNF)-alpha and IL-12/IL-23, IL-23, and IL-17 products have a category "A" recommendation as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis. Guidelines do not recommend one product over another and note the similar efficacy seen across biologics within the same class. There are no published, robust studies to support the use of more than one biologic product or targeted DMARD in combination.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 10/09/2025	Annual review of criteria performed, no changes were made
1.5	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.4	Effective Date: 12/14/2023	Annual review of criteria performed, no changes were made
1.3	Effective Date:	Annual review of criteria performed, no changes were made

	12/01/2022	
1.2	Effective Date: 02/04/2021	Removed FDA approved indications criteria, phototherapy and oral DMARD criteria for psoriasis, and added trial of one topical corticosteroid for psoriasis
1.1	Effective Date: 02/04/2021	Removal of the topical steroid criteria for psoriasis indication
1.0	Effective Date: 01/01/2021	New Policy

Imaavy™ (nipocalimab-aahu)
HCPCS: J9256

Background Information:

- Imaavy is a neonatal Fc receptor blocker indicated for the treatment of generalized myasthenia gravis (gMG) in adult and pediatric patients 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

- Myasthenia gravis (MG) is a rare autoimmune disease resulting from an immunologic attack of AChR, MuSK, and/or other receptors found on the postsynaptic neuromuscular junction. It typically presents initially as asymmetric ptosis and diplopia and is known as ocular, or class I, MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into gMG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Depending on the severity of muscle weakness, at this point MG is classified as either class II for mild, class III for moderate, and class IV for severe presentation. Those with class V disease require intubation due to profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Imaavy has only been studied in patients with class II – IV disease. There is no safety and efficacy data to support use in patients with class I or V disease at this time.

- Imaavy is only indicated for use in patients with anti-AChR or anti-MuSK antibodies. An immunologic assay to detect for the presence of anti-AChR and anti-MuSK antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has one of these antibody types, at least one other confirmatory test should be conducted. A positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) all can be used to verify anti-AChR MG. Only a repetitive nerve stimulation (RNS) or single-fiber electromyography (SFEMG) can be used to confirm anti-MuSK antibody positive disease.

- The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. MuSK antibody positive disease is not typically associated with thymic abnormalities or thymoma. The 2021 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with gMG without thymoma based on class II evidence from a meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery. Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Imaavy has not been studied in patients who have undergone thymectomy within 6 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Imaavy in these patient populations at this time regardless of antibody status.

- Safety and efficacy of Imaavy were established in the Vivacity-MG3 trial, a multicenter, randomized, double-blind, placebo-controlled study of 153 patients with gMG. Patients had class II – IV disease and were already stable on at least one treatment, which included

acetylcholinesterase inhibitors, corticosteroids, or immunosuppressants, for MG prior to study entry. They also had a myasthenia gravis activities of daily living (MG-ADL) score of at least 6. Patients were randomly assigned 1:1 to receive Imaavy plus standard of care (SOC) or placebo plus SOC. The primary endpoint was the mean change in MG-ADL score from baseline over weeks 22, 23, and 24. The trial met its primary endpoint with reductions in MG-ADL score by 4.70 points in the Imaavy plus SOC group which was significantly more than the 3.25 point improvement from baseline observed in the placebo plus SOC arm (p-value = 0.002).

- Standard therapies recommended by the 2021 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, rituximab, Soliris®, IVIG, and PLEX.

- Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.

- Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. The onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect, doses should be maintained for six months to two years of therapy and then tapered to the lowest effective dose.

- Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents that are better supported by randomized clinical trial data.

- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.

- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe gMG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last

only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. Treatment guidelines state rituximab should be considered as an early therapeutic option in patients with MuSK antibody positive MG who have an unsatisfactory response to initial immunotherapy. The efficacy of rituximab in refractory AChR antibody positive MG is uncertain. It is an option if patients fail or do not tolerate other immunosuppressive agents.

- Soliris should be considered in the treatment of severe, refractory, AChR antibody positive gMG. Until further data become available to allow comparisons of cost and efficacy with other treatments guidelines state, Soliris should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals.

- Imaavy has not been studied in combination with other medications used to treat MG such as Soliris; therefore, there is no data to support combination use of MG treatments.

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Policy History		
#	Date	Change Description
1.0	Effective Date: 09/01/2025	New Policy

Imdelltra™ (tarlatamab-dlle)
HCPCS: J9026

Background Information:

- Imdelltra is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

- Safety and efficacy were evaluated in the DeLLphi-301, a phase II, open-label, multicenter, multi-cohort study of 99 patients with relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. Patients had to have a ECOG score of 0 – 2, a platelet count greater than 100,000/µL, liver enzymes less than 5 times the upper limit of normal, and a creatinine clearance greater than 30 mL/min. They could not have HIV infection or hepatitis B or C virus infection unless the viral load was undetectable or any uncontrolled infection. Brain metastases and leptomeningeal disease must have been treated and unsymptomatic. Patients could not have myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure events, or a thromboembolic events within the 12 months prior to Imdelltra administration. Subjects had not received prior bispecific DLL3-directed CD3 T cell engager. The primary endpoints were overall response rate (ORR) and duration of response (DOR). The ORR was 40% (95% CI: 31, 51) and median DOR was 9.7 months (range 2.7, 20.7+).

- Due to the risk of cytokine release syndrome and neurological toxicities, the step-up doses of Imdelltra require patients to be monitored in an appropriate healthcare setting 22 – 24 hours post-infusion. Patients must also remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of infusion and need to be accompanied by a caregiver.

- Imdelltra has not been studied when given following prior treatment with Imdelltra or following any other DLL3)-directed CD3 T-cell engager therapy.

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Policy History		
#	Date	Change Description
1.0	Effective Date: 09/01/2025	New Policy

Imfinzi™ (durvalumab)
HCPCS: J9173

Background Information:

- Imfinzi is indicated for

  - In combination with platinum-containing chemotherapy as neoadjuvant treatment, followed by Imfinzi continued as a single agent as adjuvant treatment after surgery, for the treatment of adult patients with resectable (tumors ≥ 4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements

  - The treatment of adult patients with unresectable stage III NSCLC who's disease has not progressed following concurrent platinum-based chemotherapy and radiation

  - In combination with Imjudo and platinum-based chemotherapy, for the treatment of adult patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations

  - As a single agent, for the treatment of adult patients with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy

  - In combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive stage small cell lung cancer (SCLC)

  - In combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC)

  - In combination with tremelimumab-actl, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC)

  - In combination with carboplatin and paclitaxel followed by Imfinzi as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR)

  - In combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by single agent Imfinzi as adjuvant treatment following radical cystectomy, for the treatment of adult patients with muscle invasive bladder cancer (MIBC)

- Efficacy and safety for Imfinzi in non-small cell lung cancer was determined in the PACIFIC trial, a randomized, double-blind, placebo-controlled phase III study of 713 patients with unresectable stage III NSCLC who completed at least 2 prior cycles of concurrent platinum-based chemotherapy and radiation. Patients were randomized to Imfinzi or placebo for up to 12 months or unacceptable toxicity or progressive disease. Treatment was initiated 6 weeks following completion of chemoradiation. Patients must have had an ECOG performance status of 0 – 1 and were excluded if they required systemic immunosuppression. The primary endpoint was progression free survival which was shown to be statistically significant compared to placebo.

- Safety and efficacy for use in extensive disease small cell lung cancer was assessed in the CASPIAN trial, a phase III, randomized, active-control, open-label study of 537 patients with extensive disease small cell lung cancer. The target population included those with histologically or cytologically documented extensive disease or those with T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan. Eligible patients had an ECOG performance status of 0 – 1 and were suitable to receive platinum-based chemotherapy. Patients could not have received prior therapy and were excluded if they required systemic immunosuppression. The primary endpoint was overall survival of Imfinzi plus chemotherapy versus chemotherapy alone. The Imfinzi plus chemotherapy arm had a statistically significant overall survival rate compared to chemotherapy alone.

- Safety and efficacy for use in BTC was investigated in the TOPAZ-1 study, a randomized, double-blind, placebo-controlled, multicenter trial of 685 patients with histologically confirmed locally advanced unresectable or metastatic disease who have not previously received systemic therapy. Patients with recurrent disease greater than 6 months after surgery and/or completion of adjuvant therapy were eligible. Patients had an ECOG performance status of 0 and 1 and least one target lesion by RECIST 1.1. The primary endpoint was overall survival of Imfinzi plus chemotherapy versus chemotherapy alone. The Imfinzi plus chemotherapy arm had a statistically significant overall survival rate compared to chemotherapy alone.

- Safety and efficacy for use in HCC was established in the HIMALAYA trial, a randomized, open-label, multicenter, phase III study of 1,324 patients with unresectable, advanced HCC who had not been treated with prior systemic therapy and were not eligible for locoregional therapy. Patients were randomized to either Imfinzi alone, a single priming dose of Imjudo 300 mg added to Imfinzi 1500 mg followed by Imfinzi monotherapy every four weeks, or sorafenib 400 mg twice daily. The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented gastrointestinal (GI) bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; and active or prior documented autoimmune or inflammatory disorders. All subjects had a Child-Pugh Score class A and an ECOG performance score of 0 – 1. The primary endpoint was overall survival (OS) between the Imjudo plus Imfinzi arm versus the sorafenib arm. OS improved from a median 13.8 months with sorafenib to 16.4 months with the dual immunotherapy representing a 22% reduction in the risk for death during the

study period (HR 0.78; 95% CI: 0.66 - 0.92; p-value = 0.0035). At 3 years, OS rates were an estimated 31% with Imjudo in combination with Imfinzi versus 20% with sorafenib.

- The POSEIDON trial was a randomized, multicenter, active-controlled, open-label, phase III study of 1,013 previously untreated patients with EGFR/ALK wild-type mNSCLC. Patients were randomized to either Imjudo plus Imfinzi and platinum-based chemotherapy for up to four 21-day cycles, followed by Imfinzi once every 4 weeks until progression and one additional Imjudo dose; Imfinzi plus chemotherapy for up to four 21-day cycles, followed by Imfinzi once every 4 weeks until progression; or chemotherapy for up to six 21-day cycles. Chemotherapy options for all arms included carboplatin plus nab-paclitaxel regardless of histology, cisplatin or carboplatin plus gemcitabine for patients with squamous histology, and cisplatin or carboplatin plus pemetrexed for patients with non-squamous histology. Patients with non-squamous histology who received pemetrexed-platinum doublet could receive pemetrexed maintenance therapy if eligible. The study excluded patients with active infection, another primary malignancy, a medical contraindication to platinum-based doublet therapy, and active or prior documented autoimmune or inflammatory disorders. All subjects had an ECOG performance score of 0 – 1. The primary endpoints were progression-free survival (PFS) and OS for Imfinzi + chemotherapy versus chemotherapy. Key alpha-controlled secondary end points were PFS and OS for Imjudo plus Imfinzi and chemotherapy versus chemotherapy. PFS was significantly improved with Imfinzi plus chemotherapy versus chemotherapy (HR = 0.74; 95% CI: 0.62, 0.89; p-value = 0.0009; median 5.5 v 4.8 months); a trend for improved OS did not reach statistical significance (HR = 0.86; 95% CI: 0.72, 1.02; p-value = 0.0758; median 13.3 v 11.7 months; 24-month OS 29.6% v 22.1%). PFS (HR = 0.72; 95% CI: 0.60, 0.86; p-value = 0.0003; median 6.2 v 4.8 months) and OS (HR = 0.77; 95% CI: 0.65, 0.92; p-value = 0.0030; median 14.0 v 11.7 months; 24-month OS 32.9% v 22.1%) were significantly improved with Imjudo plus Imfinzi and chemotherapy versus chemotherapy alone.

- Safety and efficacy for use in combination with neoadjuvant chemotherapy, followed by surgery and continued adjuvant treatment with Imfinzi as a single agent was investigated in the AEGEAN trial, a randomized, double-blind, placebo-controlled, multicenter study of 802 patients with previously untreated and resectable squamous or non-squamous NSCLC. Patients were enrolled regardless of tumor PD-L1 expression. Eligible patients had no prior exposure to immune-mediated therapy, a ECOG performance status of 0 or 1, and at least one target lesion. Patients with active or prior documented autoimmune disease or use of any immunosuppressive medication within 14 days of the first dose of Imfinzi were ineligible. The primary endpoints were pathological complete response (pCR) and event-free survival. The trial demonstrated statistically significant improvements in EFS and pCR rate in the Imfinzi in combination with chemotherapy arm compared to the placebo in combination with chemotherapy arm.

- Safety and efficacy were evaluated in the ADRIATIC study, a randomized, doubleblind, placebo-controlled, multicenter study in 730 patients with histologically or cytologically confirmed LS-SCLC whose disease had not progressed following concurrent chemoradiation therapy (cCRT). Eligible patients completed cCRT consisting of 4 cycles of platinum-based chemotherapy and either 60 - 66 Gy once daily over 6 weeks or 45 Gy twice daily over 3 weeks of radiation therapy within 42 days prior to the first dose of Imfinzi or placebo. Patients with active or prior documented autoimmune disease within 5 years of initiation into the study; a history of active primary

immunodeficiency; a history of grade ≥ 2 pneumonitis or active tuberculosis or hepatitis B or C or HIV infection; or active interstitial lung disease were ineligible. Patients with mixed SCLC and NSCLC histology were also ineligible. The primary endpoints were overall survival (OS) and progression free survival (PFS). Imfinzi led to significantly longer OS than placebo (median: 55.9 months [95% CI: 37.3, NR] vs. 33.4 months [95% CI: 25.5, 39.9]; hazard ratio for death: 0.73; 98.321% CI: 0.54, 0.98; p-value = 0.01), as well as to significantly longer PFS (median 16.6 months [95% CI: 10.2, 28.2] vs. 9.2 months [95% CI: 7.4, 12.9]; hazard ratio for progression or death: 0.76; 97.195% CI: 0.59, 0.98; p-value = 0.02).

- Safety and efficacy for use in endometrial cancer were evaluated in the DUO-E trial, a randomized, multicenter, double-blind, placebo-controlled study in patients with advanced or recurrent endometrial cancer. The trial enrolled patients with newly diagnosed stage III disease or newly diagnosed stage IV disease. The trial also enrolled patients with recurrent disease with a low potential for cure by radiation therapy or surgery. For patients with recurrent disease, prior chemotherapy was allowed only if it was administered in the adjuvant setting and at least 12 months had elapsed from the date of last dose of chemotherapy to the date of relapse. Patients with endometrial sarcoma were excluded, and patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. The primary endpoint was progression free survival (PFS). Statistically significant PFS benefit was observed in the Imfinzi arm (hazard ratio [HR]: 0.71 [95% CI: 0.57, 0.89]; p-value = 0.003) and the Imfinzi + olaparib arm (HR: 0.55 [95% CI: 0.43, 0.69]; p-value < 0.0001) versus the control arm.

- Safety and efficacy for use in muscle invasive bladder cancer (MIBC) were evaluated in the NIAGRA trial, a randomized, open-label, multicenter study of 1,063 patients who were candidates for radical cystectomy and who had not received prior systemic chemotherapy or immune-mediated therapy for the treatment of NMIBC MIBC. Patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. The primary endpoint was event-free survival (EFS) with overall survival (OS) being an additional endpoint. At a pre-specified interim analysis, the trial demonstrated a statistically significant improvement in EFS and OS. Median EFS was not reached (NR) (95% CI: NR, NR) in the Imfinzi with chemotherapy arm and 46.1 months (95% CI: 32.2, NR) in the chemotherapy arm (hazard ratio 0.68 [95% CI: 0.56, 0.82]; two-sided p-value < 0.0001). Median OS was not reached in either arm (hazard ratio 0.75 [95% CI: 0.59, 0.93]; two-sided p-value = 0.0106).

- Imfinzi has not been studied as combination therapy when used to treat non-small cell lung cancer.

- There are no studies to support use of a different PD-L1 when treatment failure has occurred with another. The National Comprehensive Cancer Network guidelines also do not support use of a PD-L1 inhibitor following use of one in a prior line of therapy.

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Policy History		
#	Date	Change Description
1.7	P&T Date: 06/05/2025 Effective Date: 07/21/2025	Updated the renewal criteria to only allow for only 24 months of therapy for metastatic non-small cell lung cancer and added the trial and failure of preferred products statement
1.6	Effective Date: 02/13/2025	Annual review of criteria was performed, no changes were made
1.5	Effective Date: 02/08/2024	Updated to remove indication specific criteria and list FDA approved indications and NCCN guideline recommendations
1.4	Effective Date: 02/02/2023	Updated to include the new indication of metastatic non-small cell lung cancer and updated renewal authorization to allow no less than 60 days of authorization
1.3	Effective Date: 12/01/2022	Updated to include the new indications for biliary tract cancer and hepatocellular carcinoma and reflect an authorization period of at least 60 days
1.2	Effective Date: 06/09/2022	Updated approval length to allow for FDA recommended dosing or up to 6 months at a time
1.1	Effective Date: 06/10/2021	Removed indication for urothelial carcinoma as it is no longer FDA approved and updated renewal authorization to 6 months
1.0	Effective Date: 01/01/2021	New Policy

Immune Globulin Replacement Therapy Medication Use Guidelines

Alyglo™ J1552
Asceniv™ J1599, J1554
Bivigam® J1556
Carimune® NF J1566
Cutaquig® J1599
Cuvitru™ (SC only) J1555
Flebogamma® DIF J1572
GamaSTAN® S/D (IM) J1460/J1560 CPT /90281
Gammagard® Liquid (IV & SC) J1569
Gammagard Liquid ERC® J1599
Gammagard® S/D J1566
GammakedTM (IV & SC) J1561
Gammaplex® J1557
Gamunex®-C (IV & SC) J1561
Hizentra® (SC only) J1559
HyQvia® (SC only) J1575
Octagam® J1568
Panzyga® J1576
Privigen® J1459
Qivigy® (immune globulin (human-kthm) 10%) J1599
Xembify® J1558
Yimmugo® J3590

Background Information:

- Acquired hemophilia A (AHA)

  - Acquired hemophilia A is characterized by neutralizing autoantibodies against factor VIII (FVIII). It is a rare disorder typically affecting pregnant women and those over the age of 60 years. Approximately half of patients have concomitant disorders, most often other autoimmune disorders or malignancy. In approximately 1 – 5% of cases, diagnosis occurs during pregnancy or within 1 year following childbirth. The bleeding phenotype of acquired FVIII inhibitors is variable ranging from life-threatening bleeds to mild or no bleeding. Subcutaneous hematomas are characteristic of AHA and can be the first indication of the disease.

- The 2020 International Recommendations on the Diagnosis and Treatment of Acquired Hemophilia A and the 2017 Updated Review of Evidence and Treatment Guidance state AHA should be considered in patients with recent onset of abnormal bleeding, an isolated prolongation in activated partial thromboplastin time (aPTT), and normal prothrombin time (PT). It should also be considered in nonbleeding patients not on anticoagulation, with an isolated prolonged aPTT, a mixing study consistent with an inhibitor, and a negative lupus anticoagulant (LA). Diagnosis is confirmed when FVIII activity is less than 50% of normal for the laboratory reference range and the patient has an anti-human factor VIII inhibitor level greater than 0.6 BU/mL.

- Immunosuppression therapy should be started in all adult patients with the goal of therapy to reduce the risk of bleeding by shortening the time to remission. Both the 2017 and 2020 guidance for treatment of AHA recommend use of corticosteroids alone or in combination with either cyclophosphamide or rituximab as first-line therapy. The 2020 guidelines recommend use of steroids alone in patients with FVIII level greater than or equal to 1% and an anti-human factor VIII inhibitor level less than or equal to 20 BU/mL. For patients with a FVIII level less than 1% and an anti-human factor VIII inhibitor level greater than 20 BU/mL, combination therapy should be started immediately. Therapy should continue for at least 4 weeks as 60 – 80% of patients will see an improvement in FVIII activity levels within that timeframe.

- Use of immunoglobin therapy is not recommended by either the 2020 or the 2017 guidance. However, it has been shown to possible be efficacious when used as part of the modified Bonn-Malmo Protocol (MBMP). The protocol combines immunoadsorption for inhibitor elimination, factor VIII substitution, intravenous immunoglobulin, and immunosuppression. During this protocol, patients received 0.3 g/kg/day of IVIG on days 5 – 7 of each 7 day treatment cycle. Treatment cycles were repeated several times, depending on the clinical response and the coagulation factor activity. In addition, one prospective, multicenter study of high-dose IGIV in 19 patients with AHA has been conducted. Patients received induction therapy with IGIV at a dose of 1,000 mg/kg x 2 consecutive days or 400 mg/kg x 5 consecutive days followed by maintenance doses at intervals as clinically indicated. The study showed some patients may experience beneficial effects and a decrease in anti-human factor VIII inhibitor levels with the use of IVIG.

- Allogeneic bone marrow transplant (BMT) recipients or patients treated with an anti-CD19 directed chimeric antigen receptor T-cell therapy (CAR-T)

  - Allogenic bone marrow transplant patients receive stem cells from another individual, either a matched related or an unrelated donor. These patients require both long- and short-term infection prevention measures depending on their degree of immunosuppression. Infection is the primary cause of death in approximately 17% to 20% of allogenic BMT patients. Treatment plans for infection prevention include individualized antimicrobial therapy, along with IVIG in select patients.

  - International Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients (2009) recommend against the routine use of IVIG within the first 100 days after BMT, citing a meta-analysis of randomized controlled trials showing no improvement in survival, infection prevention, or other transplant complications. In BMT patients with severe

hypogammaglobulinemia, evidenced serum IgG less than 400 mg/dL, IVIG is recommended for the prevention of bacterial infection. Guidelines recommend against its use beyond 100 days after BMT in patients without severe hypogammaglobulinemia.

- Recommended dosing for adult or adolescent BMT patients with severe hypogammaglobulinemia is 500 mg/kg/week. Recommended dosing for pediatric BMT patients with severe hypogammaglobulinemia is 400 mg/kg/week. Guidelines suggest monitoring serum IgG levels every 2 weeks for patients receiving IVIG therapy.

- Autoimmune encephalitis

  - The autoimmune encephalitis syndromes have a wide clinical spectrum that ranges from typical limbic encephalitis to syndromes with complex neuropsychiatric symptoms such as deficits of memory, cognition, psychosis, seizures, abnormal movements, or coma. This group of disorders is associated with antibodies to neuronal cell surface/synaptic proteins. The target antigens usually play critical roles in synaptic transmission and plasticity. Clinical features include prodromal headache, fever, prominent psychiatric manifestations, insomnia, memory deficits, seizures, decreased level of consciousness, frequent dyskinesias, autonomic instability, and language dysfunction.

    - Autoimmune encephalopathy should be suspected in those with symptoms accompanied by cerebrospinal fluid (CSF) lymphocytic pleocytosis or oligoclonal bands; electroencephalography (EEG) with infrequent epileptic activity but frequent slow, disorganized activity that does not correlate with most abnormal movements; and brain magnetic resonance imaging (MRI) that is often normal or shows transient fluid-attenuated inversion recovery (FLAIR) or contrast-enhancing abnormalities in cortical (brain, cerebellum) or subcortical (hippocampus, basal ganglia, white matter) regions. CSF examination should be performed to evaluate for antibodies and should include cell count, protein, glucose, and viral cultures. Studies to exclude other pathogens should also be performed. EEG should be performed to exclude nonconvulsive seizures. In patients with paraneoplastic and autoimmune encephalitis, nonspecific EEG abnormalities are common and include focal or generalized slowing, epileptiform activity, and periodic lateralized epileptiform discharges (PLEDs). MRI is helpful in this clinical setting to exclude a cerebrovascular event or metastatic disease among others. Characteristic MRI findings in patients with paraneoplastic or autoimmune encephalitis include signal hyperintensities on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images in affected brain regions (eg, medial temporal lobes and/or brainstem); subcortical regions and the cerebellum are sometimes affected as well.

- The differential diagnosis of this clinical presentation includes primary psychiatric disorders, malignant catatonia, neuroleptic malignant syndrome, viral encephalitis, and encephalitis lethargica and should be ruled out before confirming a diagnosis of autoimmune encephalitis.

    - Based on observational studies and clinical experience, initial treatment with intravenous methylprednisolone and either 400 mg/kg IVIG per day for five days or plasma exchange in most patients. An alternative approach to stepwise escalation of immunotherapy is to use rituximab in combination with steroids and IVIG or plasma exchange as initial therapy. This approach is gaining favor in severely affected patients based on clinical experience and accumulating data supporting the effectiveness of rituximab in reducing relapses when used in the second-line setting.

- Autoimmune hemolytic anemia (AIHA)

- AIHA is a decompensated acquired haemolysis caused by the host's immune system acting against its own red blood cell antigens. Warm AIHA is the most common type and is caused by antibodies that are active at body temperature. Patients may present with symptoms of anemia, hemolysis, pallor, splenomegaly, hepatosplenomegaly, or hemoglobinuria. Specific symptoms that occur may vary from one person to another and may depend upon the rate of onset, the rate of destruction of healthy red blood cells and the presence of an underlying disorder.

- The 2017 British Diagnosis and Management of Primary Autoimmune Hemolytic Anemia guidelines state AIHA should be suspected based upon a thorough clinical evaluation, a detailed patient history, identification of characteristic symptoms, and a variety of tests. To confirm a diagnosis of warm AIHA, patients should have a hemoglobin less than 10 g/dL and also symptoms of hemolysis including increased bilirubin, increased reticulocytes, decreased haptoglobin, normal or elevated lactate dehydrogenase, urinary hemosiderin, and/or blood in the urine. In addition, guidelines state patients should have a direct agglutination (Coombs) test performed and it should show they are positive for IgG autoantibodies.

- Immunosuppression therapy should be started in all patients with the goal of therapy to induce remission. The 2017 guidance for treatment of AIHA recommend use of corticosteroids alone as first-line treatment. If there is no response to steroids, rituximab should be started as second-line therapy. Third-line therapies include azathioprine, cyclosporin, danazol, mycophenolate mofetil, or splenectomy. The half-life of autoantibodies is approximately 2 – 3 weeks, so even if therapy halts production of autoantibodies, patients may still experience hemolysis for 2 – 3 weeks following therapy initiation. Therefore, patients should try each line of therapy for at least 21 days before failure is considered.

- Regular use of immunoglobin therapy is not recommended by the 2017 guidance. However, the guidelines do state IVIG may be useful in emergency situations. Evidence from case studies suggest 40% of patients respond to IVIG 0.4 – 0.5 g/kg/day for 5 days and most responders maintained their hemoglobin levels for greater than or equal to 3 weeks. Emergent treatment with IVIG is considered in the guidelines as short term treatment when patients have a pre-treatment hemoglobin level of less than 6 g/dL or as a temporizing measure prior to splenectomy.

- Dermatomyositis

- Dermatomyositis (DM) is an idiopathic immune-mediated myopathy that can occur in children and adults. It commonly presents with progressive, symmetric, proximal muscle weakness and muscle inflammation that can affect a patient's ability to walk, run, and pick themselves up after a fall. Weakness typically begins with muscles closest to and within the trunk of the body, such as the neck, hip, back, and shoulder muscles. In addition to muscle symptomology, patients with DM typically present with a rash which is a key distinguishing feature of DM compared to polymyositis. Pathognomonic cutaneous features of DM are a heliotrope rash and Gottron's papules. Gottron's papules may resemble lesions of lupus erythematosus, lichen planus, or psoriasis; however, a heliotrope rash is rare in other disorders and therefore highly suggestive of dermatomyositis if present. Additional characteristic cutaneous features of DM include Gottron's sign, photodistributed erythema, nailfold changes, poikiloderma, psoriaform changes in the scalp, and calcinosis cutis. Systemic manifestations may also occur and include, but are not limited to, gastrointestinal ulcers, interstitial lung disease, dysphagia, and malignancy in adults. Most patients with DM exhibit both cutaneous disease and muscle weakness (classic DM), though the onset of cutaneous manifestations can precede myositis by several months in 30% of these patients or follow shortly after muscle involvement in about 10%. Cutaneous manifestations of DM may persist after successfully treating DM-associated myositis in patients with classic DM; these patients are termed as having post-myopathic DM. Additionally, a subset of patients may develop the characteristic cutaneous manifestations in the absence of muscle symptoms or related laboratory findings. These patients have a distinct form of DM referred to as clinically amyopathic DM and account for about 20% of patients with DM.

- Diagnosis of DM is primarily clinical, generally depending on the presence of characteristic clinical and laboratory findings and may include laboratory tests, imaging studies, electromyography (EMG), and skin and/or muscle biopsy. Tests needed to aid in establishing a diagnosis vary between groups of patients depending on their presentation (i.e. highly characteristic clinical presentation, muscle weakness and nonspecific but typical findings, atypical findings, or cutaneous features without weakness). It is essential that DM be distinguished from other conditions that cause muscle weakness and/or a similar cutaneous presentation. Differential diagnoses may include but are not limited to drug-induced myopathy, myasthenia gravis, discoid lupus erythematosus, lichen planus, psoriasis, rosacea, sarcoidosis, discoid lupus erythematosus, graft versus host disease, subacute cutaneous lupus erythematosus, systemic lupus erythematosus, and tinea corporis.

- Classification criteria have been used historically for diagnostic purposes. These criteria have defined DM primarily for clinical and epidemiologic research and are useful for clinicians to identify key features of disease; however, there are limitations to the sensitivity and specificity of these criteria for diagnostic purposes. Additionally, there is a lack of consistency as several sets of classification criteria have been published throughout the literature.

- The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) revised classification criteria for adults and juvenile idiopathic inflammatory myopathies in 2017, which classifies patients as having definite, probable, and possible disease based on a score and corresponding probability of disease with two different scoring systems depending on whether a muscle biopsy was performed. The criteria include four variables related to muscle weakness, three related to skin manifestations, and others related to lab findings and other

clinical manifestations. If a patient meets classification criteria for IIM, a classification tree further subclassifies patients as having amyopathic DM, DM, or juvenile DM.

- The Myositis Association lists comprehensive diagnostic criteria on their website both for classic DM, amyopathic DM, and juvenile DM that has been developed based on research data and expert clinical experience.

- Different DM expert groups have proposed classification criteria for DM that solely presents with cutaneous manifestations. A group of dermatology experts suggest biopsy-confirmed hallmark cutaneous manifestations of classic DM occurring for six months or more, no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities for at least 6 months, absence of exclusion criteria (i.e. systemic immunosuppressive therapy, use of drugs that may produce DM-like skin changes), and normal results for more extensive muscle testing if pursued. An expert group of neurologists and rheumatologists proposed similar criteria but also included electrophysiologic studies in their classification criteria.

- The goals of treatment are to improve muscle strength, to avoid the development of extramuscular complications, and resolution of cutaneous disease manifestations. Cutaneous manifestations of DM frequently respond to agents used to treat the associated myositis; however, they can persist despite the myositis effectively being treated and may require additional treatment.

- Glucocorticoids are considered first-line therapy. They are typically initiated with prednisone at a dose of 1 mg/kg per day (maximum daily dose of 80 mg) in adults and 2 mg/kg per day (maximum daily dose of 80 mg) in pediatric patients. A steroid-sparing immunosuppressive agent is generally started along with glucocorticoid treatment so the patient can eventually begin to taper their steroids. Methotrexate or azathioprine are the recommended steroid-sparing immunosuppressive agents for adults, while methotrexate is preferred for pediatric patients with cyclosporine as an alternative. Tapering of glucocorticoids is based on a combination of the improvement in muscle enzymes and recovery of muscle strength. Ideally, normalization of enzymes and complete recovery of muscle strength should occur before glucocorticoids are tapered. The initial response to glucocorticoids in the patient with DM typically takes four to six weeks for normalization of creatine kinase (CK) levels or three to four months to regain muscle strength.

- Some patients either relapse after an initial response to therapy or fail to respond to glucocorticoids and immunosuppressant therapy. These patients are considered to have recurrent or resistant disease. IVIG is considered the next step when the patient experiences recurrent or resistant disease after glucocorticoids and immunosuppressant therapy, and its use for refractory DM in adults is supported by the 2012 American Academy of Neurology guidelines for IVIG in the treatment of neuromuscular disorders.

- The efficacy of IVIG in adults was demonstrated in a double-blind, placebo-controlled trial of 15 DM patients with resistant disease who continued prednisone and were randomly assigned to a monthly IVIG infusion (2 g/kg) or placebo for 3 months. Patients assigned to IVIG all had significant improvement in their muscle strength and neuromuscular symptom scores.

- The benefits of IVIG in pediatric patients has been reported in multiple observational studies of children with juvenile DM who previously failed glucocorticoid therapy and in the majority of cases immunosuppressants as well. Reported patients experienced improvement in skin disease and muscle strength; additionally, use of IVIG reduced the cumulative glucocorticoid dose for most patients. IVIG was commonly dosed at 2 g/kg (maximum dose 70 g) as a single dose every two weeks for three doses, then monthly according to the childhood arthritis and rheumatology research alliance (CARRA) consensus clinical treatment plans for juvenile DM.

- Other therapies that have been shown to have some effectiveness in adults with refractory DM either alone or in combination with other treatment modalities include cyclosporine, mycophenolate mofetil, chlorambucil, and cyclophosphamide. For pediatric patients, cyclosporine has also shown some effectiveness in refractory juvenile DM, while a number of other therapies are considered investigational and require further studies to determine their role in juvenile DM.

- Adult patients with amyopathic DM or post-myopathic DM with persistent cutaneous lesions require additional treatment. A multifaceted approach is generally necessary to achieve a response for cutaneous DM. This includes photoprotection, antipruritic agents, topical corticosteroids or topical calcineurin inhibitors, and systemic medications. Skin lesions of DM are often resistant to photoprotection and topical therapies alone, therefore necessitating initiation of systemic therapy. Glucocorticoids have limited evidence for efficacy for cutaneous DM and are not generally advised if they are no longer required for extracutaneous manifestations of DM. For mild cutaneous DM (< 10% BSA, minimal pruritis), hydroxychloroquine is suggested as initial systemic therapy. Response should be evident after 6 - 12 weeks of treatment with a 3 month trial appropriate to assess treatment efficacy. Methotrexate may be added for patients whose response to hydroxychloroquine is inadequate or used alone if hydroxychloroquine cannot be tolerated. For severe cutaneous DM (> 10% BSA involvement, intolerable pruritis, or otherwise disabling disease) methotrexate is recommended as initial systemic therapy with improvement expected within 8 - 12 weeks. Hydroxychloroquine may subsequently be added if there is an insufficient response to methotrexate or the two can be started simultaneously depending on the clinician's experience. Once a satisfactory response is achieved with hydroxychloroquine or methotrexate and is maintained for several months, slow tapering should be initiated to the lowest dose necessary to maintain the response.

- Patients with amyopathic DM or post-myopathic DM who fail to respond to methotrexate and/or hydroxychloroquine or who relapse after an initial response have refractory cutaneous disease and require more aggressive immunomodulatory and immunosuppressive agents. IVIG and mycophenolate mofetil are considered treatments of choice for cutaneous DM refractory to conventional therapies. Comparative studies have not been performed between these agents.

- IVIG is administered monthly as a 2 g/kg infusion with clinical improvement expected within 2 - 3 cycles, but full benefit to be realized after about 6 months. The interval between treatments is typically lengthened in a progressive fashion once the patient is at a complete or near complete clinical response, however, relapse may occur upon treatment discontinuation. Improvement in cutaneous DM was reported in a randomized, placebo-controlled trial evaluating 2 g/kg IVIG monthly for DM-related myositis. Marked improvement in skin disease occurred in

8 of 12 patients treated with IVIG in either the initial or crossover phase of the trial with improvement evident 15 days after the first infusion and peaking between the second and third. Retrospective studies, case reports, and case series further support IVIG in refractory DM.

- Mycophenolate mofetil for cutaneous DM is supported by uncontrolled studies and a case series. These studies suggest higher doses may be required to effectively treat cutaneous manifestations of DM. Mycophenolate mofetil is started as 500 mg twice daily for two weeks then titrated, if tolerated, up to 1.5 g twice daily with improvement in skin disease expected within two to three months of treatment. Due to the slow onset of action, overlapping treatment (i.e. with methotrexate) may reduce the risk of disease flares during titration. If the response is poor after three months, transitioning to alternative treatment is recommended.

- Other therapies for refractory cutaneous DM may include azathioprine, cyclosporine, cyclophosphamide, chlorambucil, and dapsone. There is a lack of strong evidence supporting these therapies which, along with the serious adverse effect profile associated with many of these agents, suggests that they may best be suited for patients who have failed or cannot receive IVIG or mycophenolate mofetil.

- Fetal alloimmune thrombocytopenia

- Fetal alloimmune thrombocytopenia is the most common type of severe thrombocytopenia in fetuses and neonates. It results from incompatibility between parents for platelet-specific antigens. These antigens are inherited in the fetus in an autosomal codominant fashion. Fetal-maternal passage of platelets leads to the development of specific antibodies to the exposed antigen in the pregnant patient.

- The diagnosis is usually made after an affected pregnancy when either severe unexplained thrombocytopenia presents in a neonate or fetal or neonatal intracranial hemorrhage is diagnosed in the presence of thrombocytopenia. Confirmation of the diagnosis requires both demonstration of platelet-specific antigen incompatibility between the parents or between the mother and the neonate and the presence of maternal antibodies against the involved antigen. The most significant complication of fetal alloimmune thrombocytopenia is intracranial hemorrhage.

- Because the majority of intracranial hemorrhages occur before the onset of labor, treatment must be initiated antenatally to prevent them. Treating the mother with IVIG is the mainstay of therapy for fetal alloimmune thrombocytopenia. Depening of the severity of disease in prior pregnancies, the 2011 Fetal and Neonatal Alloimmune Thrombocytopenia Management Algoirithm recommend initiation of therapy should begin at different gestational timeframes.

- When the mother has had an infant with thrombocytopenia but no intracranial hemorrhage, IVIG should be started at 20 weeks gestation at a dose of 2 g/kg/week or 1 g/kg/week with 0.5 mg/kg/day of prednisolone. At 32 weeks gestation, the dose of IVIG is increased to 2 g/kg/week and should be given with 0.5 mg/kg/day of prednisolone.

- When the mother has had a previous fetus or neonate with intracranial hemorrhage diagnosed at 28 or more weeks of gestation, IVIG should be initiated at a dose of 1 g/kg/week at 12 weeks gestation. At 20 weeks, the dose of IVIG can be increased to 2 g/kg/week or 0.5 mg/kg/day prednisolone can be added to the patient's drug regimen. At 28 weeks gestation, the patient should receive 2 g/kg/week IVIG with 0.5 mg/kg/day prednisolone.

- When the mother has had a previous fetus with intracranial hemorrhage diagnosed at less than 28 weeks of gestation, IVIG should be initiated at a dose of 2 g/kg/week at 12 weeks gestation. At 20 weeks gestation, 1 mg/kg/day prednisolone should be added to the patient's drug regimen until delivery.

- HIV infected children

    - HIV infected children are at increased risk of infections and prevention of infections is a critical component of care.

    - Current guidelines, encompassing recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics, strongly recommend IVIG use among HIV-infected children who have hypogammaglobulinemia to prevent serious bacterial infections (SBIs). The recommendation is based on evidence from trials where IVIG has been shown to decrease the frequency of bacterial infections, increase the time free from serious bacterial infections, and decrease the frequency of hospitalization in children with AIDS. The guidelines cite the supporting evidence is from studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents.

    - The recommended dose is 400 mg/kg every 2-4 weeks to maintain the serum IgG level.

- Hypogammaglobulinemia associated with either chronic lymphocytic leukemia (CLL), multiple myeloma, or anti-CD20 monoclonal antibody treated B-cell lymphoma

- Chronic lymphocytic leukemia

    – Chronic lymphocytic leukemia patients are at increased risk of infections and require management with infection prevention and antibiotic prophylaxis. Infections are the most common complication and cause of death in CLL patients. Patients with advanced disease and hypogammaglobulinemia are at in increased risk of serious infections.

    – National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia 2020 guidelines recommend IVIG in CLL patients with reduced serum IgG levels and recurrent infections requiring intravenous antibiotics or hospitalization. It is only recommended in patients

with severe hypogammaglobulinemia, evidenced by serum IgG less than 400 - 500 mg/dL. Recommended dosing is 400 mg/kg every 4 weeks. Patients should receive concomitant prophylactic antibiotic therapy in accordance with the 2020 NCCN guidelines for Prevention and Treatment of Cancer-Related Infections.

- In addition, American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend IVIG in patients with CLL with recurrent serious bacterial infections, along with reduced IgG, and subprotective antibody levels following diphtheria, tetanus, or pneumococcal immunizations. Monitoring of serum IgG levels during treatment is recommended to determine the need for continuation of therapy.

- Multiple myeloma

- Patients with multiple myeloma are at an increased risk of infections throughout the stages of the disease. Infections are a significant cause of morbidity and mortality in these patients, particularly those with advanced disease and hypogammaglobulinemia. Comprehensive treatment plans include infection prevention precautions, prophylactic antibiotics, and, in select patients, IVIG.

- The 2020 Multiple Myeloma NCCN treatment guidelines recommend considering IVIG for patients with reduced serum IgG levels and recurrent, life-threatening infections. It is only recommended in patients with severe hypogammaglobulinemia, evidenced by serum IgG less than 400 - 500 mg/dL. Recommended dosing is 400 mg/kg every 4 weeks. Patients should receive concomitant prophylactic antibiotic therapy in accordance with the 2020 NCCN guidelines for Prevention and Treatment of Cancer-Related Infections.

- American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend IVIG in patients with recurrent serious bacterial infections and sub protective antibody levels following diphtheria, tetanus, or pneumococcal immunizations. This recommendation is based off a meta-analysis and systematic review showing a reduction in serious infections and mortality in patients receiving IVIG.

- B-cell lymphoma

- Patients with B-cell lymphoma who are being treated with an anti-CD20 monoclonal antibody or CAR-T therapy are at an increased risk of infections due to the cytotoxic nature of their treatment. Infections are a significant cause of morbidity and mortality in these patients, particularly those with advanced disease and hypogammaglobulinemia. Comprehensive treatment plans include infection prevention precautions, prophylactic antibiotics, and, in select patients, IVIG.

- The 2020 B-cell lymphoma NCCN treatment guidelines state patients on these therapies may experience hypogammaglobulinemia and recommend IVIG for patients with reduced serum IgG levels and recurrent, life-threatening infections. Recommended dosing is 400 mg/kg every 4 weeks. Patients should receive concomitant prophylactic antibiotic therapy in accordance with the 2020 NCCN guidelines for Prevention and Treatment of Cancer-Related Infections.

- Hypogammaglobulinemic neonates

  - Preterm and low birth weight infants are deficient in IgG and often cared for in intensive care units, where they are at risk for sepsis. IVIG has been studied as an immune enhancing agent to reduce the risk of sepsis in these settings. In a study of patients with very low birth rate, defined as 700 grams to 1,300 grams, the prevalence of sepsis was reduced within the first 30 days of life. Typically, in clinical practive, physicians treat all patients with a birth weight of less than 1500 grams with IVIG. However, a more recent Cochrane review concluded that IVIG was not associated with a reduction in mortality, although it was associated with a 3% reduction in sepsis and 4% reduction in 1 or more episodes of a serious infection.

  - American Academy of Allergy, Asthma, and Immunology 2016 guidelines state that the use of prophylactic IVIG may provide benefit in preventing sepsis for preterm infants. While the routine use of IVIG in neonates for the prevention of infection is not recommended, high-risk patients in acute care settings may benefit from therapy. Published studies have shown IVIG dosing of 0.5 g/kg to 2 g/kg weekly for approximately 4 weeks to be safe and effective.

- Inflammatory demyelinating polyneuropathy (acute)

  - Historically, Guillain-Barré syndrome (GBS) was considered a single disorder. It now is recognized as a heterogeneous syndrome with several variant forms. Each form of GBS has distinguishing clinical, pathophysiologic, and pathologic features. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form in the United States and Europe, representing approximately 85% - 90% of cases. The typical clinical features are a progressive, fairly symmetric, muscle weakness accompanied by absent or depressed deep tendon reflexes. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles. Severe respiratory muscle weakness necessitating ventilatory support develops in about 30% of patients and dysautonomia occurs in 70% of patients. GBS usually progresses over a period of about two weeks.

  - The initial diagnosis of GBS is based upon clinical presentation. The certainty of the diagnosis is supported if cerebrospinal fluid (CSF) analysis and electrodiagnostic studies showing abnormalities typical of GBS. Therefore, these studies should be performed in all patients with suspected GBS. Lumbar puncture often reveals an elevated CSF protein with a normal CSF white blood cell count. This finding, known as albuminocytologic dissociation, is present in 50% - 66% of patients with GBS in the first week after the onset of symptoms and greater than or equal to 75% of patients in the third week. Nerve conduction studies (NCS) and needle electromyography (EMG) are valuable for confirming the diagnosis of GBS and for providing some information regarding prognosis. In addition, electrodiagnostic studies are useful in classifying the main variants of GBS as demyelinating (eg, acute inflammatory demyelinating polyneuropathy) or axonal (eg, acute motor axonal neuropathy). Demyelinating forms of GBS are supported by features

of demyelination including decreased motor nerve conduction velocity, prolonged distal motor latency, increased F wave latency, conduction blocks, and temporal dispersion.

  - The main modalities of therapy for Guillain-Barré syndrome (GBS) are plasma exchange and administration of IVIG. Patients recover sooner when treated early. IVIG is recommended in nonambulatory patients within 4 weeks of neuropathic symptom onset, and in ambulatory patients who are not yet recovering within 4 weeks of neuropathic symptom onset. The beneficial effects of plasma exchange and IVIG are believed to be equivalent while combining the two treatments is not beneficial. Intravenous immune globulin is given for five days at 0.4 g/kg per day.

- Inflammatory demyelinating polyneuropathy (chronic, CIDP)

  - CIDP, also known as chronic inflammatory demyelinating polyradiculoneuropathy, is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots. It is characterized by a relapsing-remitting or progressive course, glucocorticoid responsiveness, and electrodiagnostic or pathologic features of demyelination. In its classic form, CIDP manifests as a symmetric, motor-predominant neuropathy that results in both proximal and distal muscle weakness. Recognized variants include asymmetric and/or sensory-predominant forms. All share the common pathophysiology of inflammatory demyelination. Although relatively rare, CIDP is important to recognize among the varied causes of polyneuropathy as it is treatable with immunomodulatory therapies.

  - There is a temporal continuum between acute inflammatory demyelinating polyneuropathy (AIDP), which is the demyelinating form of Guillain-Barré syndrome (GBS), and CIDP. The time course of progression and the occurrence of relapses are used to distinguish between these entities. GBS commonly reaches its nadir within three to four weeks but does not progress beyond eight weeks. CIDP continues to progress or has relapses for greater than eight weeks. GBS is typically monophasic, but up to two relapses in the first eight weeks from onset can occur. Three or more relapses in the first eight weeks is highly suggestive of acute CIDP. Relapses closer to the eight week time period is more suggestive of CIDP.

  - The diagnosis of CIDP should be considered in patients presenting with a progressive or relapsing-remitting polyneuropathy involving both motor and sensory axons along with areflexia, particularly when weakness predominates and affects proximal and distal muscles simultaneously and symmetrically. While the initial suspicion for CIDP is clinical, the diagnosis is confirmed by evidence of peripheral nerve demyelination, which must be demonstrated by electrodiagnostic findings or rarely by nerve biopsy, and exclusion of other disorders that may cause or mimic CIDP.

    - Electromyography (EMG) should be performed in all patients with suspected CIDP and is a critical component of the evaluation. The characteristic electrophysiologic features of a definitive CIDP diagnosis per the EFNS/PNS guidelines are those of peripheral nerve demyelination which include at least one of the following:

- Greater than or equal to 50% prolongation of motor distal latency above the upper limit of normal in two nerves

- Greater than or equal to 30% reduction of motor conduction velocity below the lower limit of normal in two nerves

- Greater than or equal to 20% prolongation of F-wave latency above the upper limit of normal in two nerves or greater than 50% if the amplitude of the distal negative peak compound motor action potention (CMAP) is less than 80% of the lower limit of normal

- Absence of F waves in two nerves, if these nerves have amplitudes of distal negative peak CMAPs greater than or equal to 20% of the lower limit of normal, plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve

- Partial motor conduction block, defined by a greater than 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal, in two nerves, or in one nerve plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve

- Abnormal temporal dispersion, defined by a greater than 30% duration increase between the proximal and distal negative peak CMAP in at least two nerves

- Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in at least one nerve (median greater than or equal to 6.6 ms, ulnar greater than or equal to 6.7 ms, peroneal greater than or equal to 7.6 ms, tibial greater than or equal to 8.8 ms) plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve

- The EFNS/PNS guidelines state probable CIDP is considered when patients have greater than or equal to 30% amplitude reduction of the proximal negative peak CMAP relative to the distal, excluding the posterior tibial nerve, if the distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal in two nerves or in one nerve plus at least one other demyelinating parameter meeting any of the definite criteria in at least one other nerve.

- Cerebrospinal fluid (CSF) analysis is recommended in patients with probable CIDP and particularly for patients in whom the clinical and electrophysiologic findings are inconclusive. Albuminocytologic dissociation is a hallmark of CIDP and represents supportive evidence in the EFNS/PNS diagnostic criteria for probable CIDP.

- Magnetic resonance imaging (MRI) with gadolinium of the spine (including spinal roots, cauda equina), brachial plexus, lumbosacral plexus, and other nerve regions can be used to look for enlarged or enhancing nerves. MRI abnormalities are useful as supportive criteria for probable CIDP in the EFNS/PNS guideline.

- The initial dose of IVIG is 2 g/kg infused over two to five days (eg, 0.4 g/kg per day for five days). Many patients with CIDP require a treatment trial of repeat IVIG dosing every two to six weeks depending on clinical course.

- Idiopathic thrombocytopenia purpura (ITP, acute)

  - Immune thrombocytopenia (ITP), defined as a platelet count less than 100,000/μL, is an acquired form of thrombocytopenia that is primarily due to autoantibody-mediated destruction of platelets. The autoantibodies may also affect megakaryocytes and impair platelet production. ITP is a diagnosis of exclusion, characterized by isolated thrombocytopenia without a clinically apparent condition responsible for the low platelet count; there are no reliable laboratory tests to confirm the diagnosis.

    - The time elapsed since diagnosis determines whether ITP is referred to as newly diagnosed, persistent, or chronic. Patients are considered newly diagnosed up to three months since diagnosis. Patients have persistent disease if they are still experiencing low platelet counts in the 3 to 12 month timeframe from diagnosis. If symptoms persist more than 12 months from diagnosis, the disease is labeled as chronic.

  - The most commonly used agents for initial treatment of ITP for those who require it are glucocorticoids and IVIG. Intravenous anti-D immune globulin is a type of immune globulin that may be effective in patients who have an Rh+ blood type and have not had a splenectomy. IVIG raises the platelet count more rapidly than glucocorticoids and therefore, is often used for patients with active bleeding, patients who need an urgent invasive procedure, or patients who experience side effects with glucocorticoids. For all patients with severe bleeding and a platelet count less than 30,000/μL, immediate platelet transfusion along with ITP-specific therapy with IVIG and high-dose glucocorticoids are recommended. ITP-specific therapy should also be administered to patients with a new diagnosis of ITP and a platelet count less than 20,000/μL, even in the absence of bleeding symptoms, because the thrombocytopenia may be persistent and become more severe. Some patients with platelet counts greater than 30,000/μL may require treatment if they have an increased risk of bleeding (eg, peptic ulcer disease, high risk of falling), other hemostatic defects (eg, use of antiplatelet agents or anticoagulants), a history of bleeding at a higher platelet count, or a need for surgery/invasive procedures.

  - IVIG is administered at 1 g/kg daily for one or two days; 1 g/kg for one day is often sufficient. Alternative dosing can also be used, for example, 400 mg/kg daily for five days. The IVIG can be stopped when a response occurs even if the full course has not been completed.

- Idiopathic thrombocytopenia purpura (ITP, chronic)

    - Immune thrombocytopenia, defined as a platelet count less than 100,000/μL, is an acquired form of thrombocytopenia that is primarily due to autoantibody-mediated destruction of platelets. The autoantibodies may also affect megakaryocytes and impair platelet production. ITP is a diagnosis of exclusion, characterized by isolated thrombocytopenia without a clinically apparent condition responsible for the low platelet count; there are no reliable laboratory tests to confirm the diagnosis.

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- The threshold for pharmacologic treatment depends on multiple factors including ongoing bleeding symptoms, risk factors for bleeding, such as, sports or an active lifestyle, concomitant medical conditions and medications, anxiety, fatigue, and access to medical care. Decisions should be individualized and made in collaboration with the patient and family. Children with chronic ITP should be managed by a pediatric hematologist whenever possible.

- IVIG is considered a rescue therapy for patients with chronic ITP rather than routine, ongoing therapy. It should only be used in patients meeting the requirements for acute treatment and who have had a platelet count less than 100,000/μL for more than 12 months. The most commonly used agents for treatment of acute drop in platelets in patients with chronic ITP are glucocorticoids and IVIG. Intravenous anti-D immune globulin is a type of immune globulin that may be effective in patients who have an Rh+ blood type and have not had a splenectomy. IVIG raises the platelet count more rapidly than glucocorticoids and therefore, is often used for patients with active bleeding, patients who need an urgent invasive procedure, or patients who experience side effects with glucocorticoids. For all patients with severe bleeding and a platelet count less than 30,000/μL, immediate platelet transfusion along with ITP-specific therapy with IVIG and high-dose glucocorticoids are recommended. ITP-specific therapy should also be administered to patients with a platelet count less than 20,000/μL, even in the absence of bleeding symptoms, because the thrombocytopenia may be persistent and become more severe. Some patients with platelet counts greater than 30,000/μL may require treatment if they have an increased risk of bleeding (eg, peptic ulcer disease, high risk of falling), other hemostatic defects (eg, use of antiplatelet agents or anticoagulants), a history of bleeding at a higher platelet count, or a need for surgery/invasive procedures.

- For patients with chronic ITP whose symptoms and risks are not adequately controlled using first-line therapies and for those who remain dependent on glucocorticoid therapy to control symptoms, second-line treatments include rituximab, eltrombopag, romiplostim, and splenectomy. Other agents that are sometimes used for patients who require chronic immunosuppression include azathioprine, 6-MP, or MMF. The choice among these options is complex and highly dependent on the values and preferences of the patient and family.

- Idiopathic thrombocytopenia purpura in pregnancy

  - ITP occurs in approximately 1 to 3 in 10,000 pregnancies with only a subset of patients having platelet counts less than 50,000/μL. This is approximately 10-fold greater than the incidence of ITP in the general population which is estimated to be 3 in 100,000 adults. As in non-pregnant individuals, the risk of bleeding is greater with platelet counts less than 20,000 to 30,000/μL, although there is no absolute platelet count threshold above which bleeding does not occur. Data indicates an increased risk of bleeding if platelet count is below 20,000 to 30,000/μL for a vaginal delivery or below 50,000/μL for a cesarean section.

    - The American Society of Hematology recommends medical management of ITP in pregnancy in the following scenarios: patients are in their 3rd trimester with platelets less than 10,000/μL; platelets are 10,000 to 30,000/μL with bleeding; platelets are less than 10,000 μL after steroid failure; platelets are 10,000 to 30,000/μL and the patient is experiencing bleeding after steroid failure; and the patient is in their 3rd trimester with platelets 10,000 to 30,000 μL and asymptomatic following steroid failure.

  - Due to their efficacy and low cost, many consider corticosteroids to be first line treatment for ITP in pregnancy. However, the many adverse effects of corticosteroids are amplified during pregnancy, and pregnancy-specific toxicities such as gestational diabetes, weight gain, acceleration of bone loss, hypertension, and possibly placental abruption and premature labor must be recognized. Furthermore, some studies have associated the use of corticosteroids in the first trimester with congenital anomalies, such as orofacial clefts.

  - Alternatively, others have suggested that IVIG should be the first line therapy for pregnancy-associated ITP, especially when a long duration of therapy may not be required. Compared to corticosteroids, IVIG is less likely to induce toxicities such as hypertension. ASH guidelines consider IVIG to be an appropriate first line agent for severe thrombocytopenia, or thrombocytopenic bleeding in the third trimester. However, responses to IVIG tend to be transient, and multiple courses of therapy may be required at significant cost and patient inconvenience. Treatment with 2 g/kg IVIG infused over two to five days is an effective means of raising the platelet count rapidly.

- Kawasaki syndrome

  - Kawasaki disease (KD) is one of the most common vasculitides of childhood. KD also occurs rarely in adults. It is typically a self-limited condition with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. However, complications such as coronary artery (CA) aneurysms, depressed myocardial contractility and heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion may develop and lead to significant morbidity and mortality.

- There is no single test to diagnose KD. Diagnosis requires the presence of fever lasting greater than or equal to 5 days combined with other physical findings, without an alternative explanation, that could include bilateral bulbar conjunctival injection, oral mucous membrane changes such as fissured lips or strawberry tongue, peripheral extremity changes such as erythema of palms or soles, edema of hands or feet, polymorphous rash, cervical lymphadenopathy.

- Randomized, controlled studies and meta-analyses have confirmed that IVIG, in conjunction with aspirin, started within 10 days of fever onset reduces the risk of CA aneurysms from approximately 25% to less than 5%. IVIG has additional beneficial effects in KD, such as rapid resolution of the almost universal lymphocytic myocarditis seen in the disease. IVIG is not effective if more than ten days have elapsed from onset of symptoms. Expeditious diagnosis and timely treatment are critical to achieve the optimal clinical outcome. The usual dose of IVIG is 2 g/kg as a single dose, or 400 mg/kg daily for 5 days.

- Lambert-Eaton myasthenic syndrome (LEMS)

  - LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes. Weakness normally spreads proximally (most common in the upper arms and legs) to distally (involving feet and hands) and from the posterior towards the head, finally reaching the oculobulbar region. This is in contrast to myasthenia gravis, in which weakness typically starts in the head and then descends. The characteristic weakness is thought to be caused by antibodies generated against the P/Q-type voltage-gated calcium channel (VGCC) present on presynaptic nerve terminals and by diminished release of ACh. More than one-half of LEMS cases are associated with small cell lung cancer which expresses functional VGCC.

  - The diagnosis of LEMS is confirmed by electrodiagnostic studies including repetitive nerve stimulation and anti-P/Q-type VGCC antibody testing. The electrodiagnostic evaluation of suspected LEMS typically involves the following elements: routine motor and sensory nerve conduction studies, high-frequency repetitive nerve stimulation and/or exercise testing, and electromyography (EMG). Antibodies against the P/Q-type VGCC) are present in approximately 85% to 95% of patients with LEMS.

  - There are no clinical practice guidelines for LEMS. The most effective treatments increase the presynaptic release of acetylcholine and thereby reverse the underlying physiologic deficit present in LEMS. If adequate to induce stable functional muscle strength, no further treatment may be needed. Amifampridine is FDA approved to treat LEMS and used as a first line treatment option as it improves the release of acetylcholine. For patients who do not improve sufficiently second line treatment options include IVIG and oral immunosuppressants such as prednisone, azathioprine, mycophenolate mofetil, and cyclosporine. Some experts are reluctant to use oral immunosuppressive agents such as azathioprine in patients with cancer because of concerns that such treatment may exacerbate the malignancy.

- A number of small studies suggests benefit of IVIG in LEMS, with both clinical improvement such as improved muscle strength and a reduction in the voltage-gated calcium channel antibodies. The recommended dose of IVIG is 2 g/kg administered over 2 – 5 days every 4 - 12 weeks depending on duration of response.

- Multifocal motor neuropathy (MMN)

  - MMN is a rare disorder in which focal areas of multiple motor nerves are attacked by one's own immune system. Typically, MMN is slowly progressive resulting in asymmetrical weakness of a patient's limbs. Patients frequently develop weakness in their hand(s) causing them to drop objects or be unable to turn a key in a lock. The weakness associated with MMN can be recognized as fitting a specific nerve territory. There is essentially no objective sensory abnormalities, such as, numbness, tingling, or pain. Patients with MMN can have other symptoms, including twitching, or small random dimpling of the muscle under the skin which neurologists call fasciculations. MMN is associated with increased levels of specific antibodies to GM1, a ganglioside or sugar-containing lipid found in peripheral nerves. Elevated titers of anti-GM1 antibodies are present in 30% to 80% of patients. However, it is unclear whether anti-GM1 antibodies are involved in the pathogenesis of MMN.

    - The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) have specific requirments for the diagnosis of MMN to be made. Two core criteria must be present in a patient. The first is a slowly progressive, focal asymmetric limb weakness defined as motor involvement in the moror nerve distribution of at least two nerves for more than one month. If signs and symptoms are present only in the distribution of one nerve, only a possible diagnosis can be made. The second core criterion is a lack objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs. The diagnosis is supported by nerve conduction studies that demonstrate focal demyelination and condution block in motor nerves and normal sensory nerves. Additional supportive clinical criteria include predominant upper limb involvement, decreased or absent tendon reflexes in the affected limb, absence of cranial nerve involvement, cramps and fasciculations in the affected limb, and a response in terms of disability or muscle strength to immunomodulatory treatment. MMN can be ruled out if the patient has upper motor neuron signs, marked bulbar involvement, sensory impairment more marked than minor vibration loss in the lower lilmbs, or diffuse symmetric weakness during the initial weeks.

- MMN is treatable with IVIG. However, unlike chronic inflammatory demyelinating polyneuropathy, MMN is generally unresponsive to glucocorticoids or plasma exchange, and these therapies have been associated with clinical worsening in some cases. The EFNS/PNS and the American Academy of Neurology treatment guidelines recommend IVIG 2 g/kg given over two to five days for initial treatment of patients with MMN who require treatment due to disease progression or disability has been shown to be effective.

- Myasthenia gravis (MG)

- Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities.

- Approximately 10-15% of MG cases will become refractory resulting in profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Refractory disease is defined by the 2016 international consensus guidance for management of myasthenia gravis as worsening or unchanged disease despite use of corticosteroids and at least two different immunosuppressive therapies used in adequate doses for an adequate duration with persistent symptoms and/or side-effects that limit function.

- A proportion of patients with myasthenia gravis will experience myasthenic crisis. Impending myasthenic crisis is defined as rapid clinical worsening of myasthenia gravis that, in the opinion of the treating clinician, could lead to crisis within days to weeks. Myasthenic crisis is defined by increasing respiratory muscle and/or bulbar muscle weakness severe enough to necessitate intubation and/or mechanical ventilation. Patients experiencing symptoms of crisis should be admitted to the hospital and assessed for the need for ventilation. The 2016 international consensus guidance for management of myasthenia gravis state therapy with immunoglobulin or plasma exchange (PLEX), also known as rapid therapy, should initiated. These interventions provide a quick reversal of the exacerbation but benefits only last a few weeks. Therefore, immunosuppressive therapy should also be started to provide a longer benefit over the rapid therapies.

- The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2016 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a meta-analysis. Thymectomy should only be performed once a patient's MG has stabilized. In patient with persistent mild residual respiratory impairment or dysphagia despite treatment with pyridostigmine and immunosuppression, a course of IVIG or PLEX can be given/done preoperatively. This practice is empiric, with a goal of reducing the risk of a postoperative flare evolving quickly into myasthenic crisis. Treatment should be timed to end the week prior to surgery so that the effects of the rapid therapy peak and persist through the perioperative period.

- Standard therapies recommended by the 2016 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, IVIG, and PLEX.

- Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.

- Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect and doses should be maintained for six months to two years of therapy and then tapered to the lowest effect dose.

- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.

- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX.

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. A number of case reports and case series support the efficacy of rituximab in patients with refractory MG. In a prospective study of 22 patients with refractory MG treated with rituximab, the mean time to relapse was 17 months. Among 14 patients taking prednisone, the mean daily dose decreased from 25 mg at baseline to 7 mg after treatment with a mean follow-up of 29 months. In an observational study of 72 patients with new-onset or refractory generalized MG, those treated with low-dose rituximab had shorter time to remission, lower use of adjunctive treatments, and fewer adverse events than patients treated with conventional immunosuppressive therapy.

- Pediatric acute-onset neuropsychiatric syndrome (PANS)/pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

- PANDAS is a clinical diagnosis in children who have an acute manifestation of varied neuropsychiatric symptoms following a streptococcal (strep) infection. A child may be diagnosed with PANDAS when obsessive compulsive disorder (OCD), a tic disorder, or both suddenly appear or become worse after an illness caused by streptococci, such as strep throat or scarlet fever. The symptoms are usually dramatic, happening

"overnight and out of the blue." In addition to OCD and tics, children may become moody or irritable, experience anxiety attacks, show concerns about separating from parents or loved ones, or have issues with attention and concentration. PANS has similar features to PANDAS including OCD, eating restrictions, anxiety, attention deficit disorder, and academic decline and develops following a viral or bacterial infection. Although PANS/PANDAS are emerging autoimmune encephalopathic diseases, these two conditions are unique from autoimmune encephalitis (AE) which presents with seizures or new focal CNS findings, MRI abnormalities, and/or elevated white blood cell count in the cerebral spinal fluid. AE patients also have cognitive dysfunction whereas cognitive function remains intact with PANS/PANDAS. In addition, PANS/PANDAS patients often experience a relapsing/remitting course with rapid progression to maximum symptoms and rapid return to previous function.

- While the etiology of PANDAS is still unclear, studies suggest that the condition is brought on by a cross-reaction between antibodies to Streptococcus pyogenes and structures on neuronal cells in the brain. GABHS bacteria use molecular mimicry to appear nearly identical to molecules found in normal human tissues, thereby allowing the bacteria to evade detection for long periods of time. Once the GABHS bacteria is recognized as foreign to the body, the immune system reacts not only to the strep infection but also to the human host molecules that were mimicked. The result is an abrupt onset of PANDAS symptoms.

– PANDAS/PANS is a diagnosis of exclusion. Differentiating PANDAS from phenotypically similar conditions, such as OCD, tic disorders, and autism spectrum disorder (ASD), remains challenging and controversial due to both heterogeneous presentations and the likelihood that at least some instances of these other disorders share overlapping pathophysiology. Currently, PANDAS is characterized by five working diagnostic criteria including: OCD and/or tic disorder; pediatric onset between the age of 3 and the start of puberty; an abrupt onset and episodic course of symptoms; a temporal relationship between GABHS infection and onset and/or exacerbation; and neurologic abnormalities, such as motoric hyperactivity, choreiform movements, or tics during exacerbations. Children who present with abrupt onset of OCD and/or tic disorder, separation anxiety, or urinary frequency should be evaluated for PANDAS by testing for GABHS infection. The diagnosis is considered probable when patients present with an abrupt onset of neuropsychiatric symptoms, have evidence of recent GABHS infection, and remission of neuropsychiatric symptoms with antibiotic therapy. Because clinical diagnostic classification is challenging, more research is clearly needed to identify reliable diagnostic biomarkers of active disease including autoantibodies, inflammatory cells, metabolic profiles, and/or neuroimaging signatures. The quality of the evidence for the use of IVIG in ASD is still below what is commonly accepted for a routinely used treatment with the bulk of the studies being uncontrolled. Many studies demonstrated bias, including selection bias (lack of randomization), performance bias (lack of blinding), detection bias (lack of standardized outcomes), attrition bias (retrospective studies are prone to losing patients to follow-up), and reporting bias (case studies tend to report positive rather than negative outcomes). Thus, the current set of studies presented should be used to design and implement well-controlled, blinded randomized clinical trials in the future. Additionally, the populations used in these studies are very heterogeneous with many different immune system abnormalities, making it hard to determine if there is a particular subset of children with ASD in which the treatment may be most effective. Consensus guidelines are silent on the use of IVIG to treat symptoms related to autism.

- If PANDAS is an autoimmune disorder, and this remains controversial, then immunomodulatory treatments might be beneficial, but as of yet are unproven. Most of the medical treatment approaches targeting immune modulation are supported by weak or conflicting evidence. A recent comprehensive review by Sigra et al identified 12 treatment studies with published outcomes data. Eleven of the 12 studies were judged to have a moderate or high risk of bias, including selection bias, performance bias, detection bias, attrition, reporting bias, other bias, or a combination of these issues. The one exception was a randomized, controlled clinical trial conducted by Williams et al comparing IVIG with placebo for treatment of PANDAS OCD in 35 children which showed no difference between the IVIG and placebo groups in OCD severity scores or proportion of responders. In contrast, follow-up open-label treatment trials in these patients reported improvement in all participants regardless of their initial treatment group assignment. The follow-up data suggests patients and care givers are experiencing a placebo effect and not true treatment related resolution of symptoms.

- In addition to the Sigra et al review, Hayes completed an additional evidence-based review of the use of IVIG in PANDAS. Of the 92 records reviewed, 3 studies reported met inclusion requirements which consisted of enrollment of at least 10 patients, reporting of aggregate data for the patient population, published in 2001 or later, and assessment of patient-oriented efficacy and/or safety outcomes. The first included study by Perlmutter et al was a randomized-controlled trial of 30 pediatric patients with severe, infection-triggered exacerbations of OCD or tic disorders comparing treatment with IVIG, plasma exchange, or placebo. While results suggest that IVIG was both effective in reducing neuropsychiatric symptoms severity when compared w/ placebo, the study also had a significant number of limitations. First, there was a small sample size with no power analysis and no intent to treat analysis. Eighteen percent (3 of 17) of patients underwent additional treatment with IVIG, PE, or other additional treatments from 1 month to 1 year. Also the authors note results may not be generalizable due to strict inclusion criteria. Hayes also included the Williams et al along with the Lyon et al study. The analysis resulting in the same conclusions citing study limitations, smaller than expected effect size due to greater placebo effect and lower treatment benefit of IVIG which led to the study being underpowered. In addition, select outcome measures relied on parent report with the potential for recall bias, and the long-term outcomes may reflect benefit from the additional treatment in the follow-up months. The final study included in the Hayes report was completed by Melamed et al. It was a prospective, open-label, single-arm pretest/posttest study evaluating the use of IVIG in 21 patients with PANS. Results suggest that patients with moderate-to-severe PANS treated with IVIG experienced improvement in neuropsychological symptoms. In a subset of patients with long-term follow-up, up to 46 weeks post-treatment, symptom relief was sustained. There were significant limitations to this study as well, including no control or comparator group; a small sample size with no power analysis; an open-label trial; no intent to treat analysis; and only a subset of patients had long-term data available. Evaluating the strength of evidence in both the Sigra and Hayes reviews, there is currently insufficient data to clearly support the use of any immune modulating treatment, including IVIG, for PANDAS due to significant flaws in clinical trial design and multiple sources of bias.

- Pediatric intractable epilepsy

- Patients with epilepsy whose seizures do not successfully respond to antiseizure drug therapy are considered to have drug-resistant epilepsy (DRE). This condition is also referred to as intractable, medically refractory, or pharmacoresistant epilepsy. As many as 20% to 40% of patients with epilepsy are likely to have refractory epilepsy.

- Epilepsy surgery should be considered in appropriate patients with DRE when seizures are sufficiently frequent or severe as to significantly increase the mortality risk or disrupt the patient's quality of life. Surgery is a reasonable option for people with refractory epilepsy if seizures start in one area of the brain and that area can be removed safely. Vagus nerve stimulation (VNS) therapy is a way of controlling seizures in people who do not respond to medications and may not respond to surgery. The vagus nerve sends information from your neck down to the chest and stomach and then back up again. The vagus nerve then sends information up to the brain. Stimulation of the vagus nerve can change the likelihood of the brain to have seizures. The "classic" ketogenic diet is a special high-fat, low-carbohydrate diet that helps to control seizures in some people with epilepsy. It is prescribed by a physician and carefully monitored by a dietitian. It is usually used in children with seizures that do not respond to medications.

- The efficacy of IVIG treatment for severe childhood epilepsy was evaluated in a retrospective, multicenter study comprising 64 consecutive patients treated with IVIG for either epileptic encephalopathy or refractory epilepsy. Nine patients (14%) demonstrated complete resolution and 10 (15.6%) exhibited partial improvement. Of these 19 responders (29.7%), eight relapsed. Although IVIG is not suitable for all cases of epilepsy, it may prove efficacious for specific epileptic syndromes, mainly idiopathic West syndrome and electrical status epilepticus during sleep.

- Polymyositis (PM)

- Polymyositis is a type of inflammatory myopathy characterized by proximal skeletal muscle weakness and muscle inflammation. Muscle weakness usually happens over days, weeks, or months. It can affect a patient’s ability to walk, run, and pick themselves up after a fall. The weakness typically begins with muscles closest to and within the trunk of the body, such as the muscles of the neck, hips, back, and shoulders. The exact cause of the disease is unknown but it shares many characteristics with autoimmune disorders. In some cases, the disease may be associated with viral infections, connective tissue disorders, or an increased risk for malignancies.

- Diagnosis is based on a clinical examination that may include laboratory tests, imaging studies, electromyography (EMG), and a muscle biopsy. There is no agreed upon criteria for diagnosis with multiple methods published throughout the literature. The 2005 International Consensus Guidelines for Trials of Therapies in the Idiopathic Inflammatory Myopathies guidelines suggest diagnosis can be made with an abnormal biopsy consistent with PM and no pathognemic rash suggestive of dermatomyositis. In contrast, the Myositis Association lists comprehensive diagnostic criteria on their website stating patients should present without skin symptoms and four of the following: symmetrical muscle weakness in the shoulders/upper arms or hips/upper legs and trunk; elevated skeletal muscle-associated enzymes; muscle pain on grasping or spontaneous pain; a triad of muscle-related changes on EMG including short, small, low-amplitude polyphasic

motor unit potentials, fibrillation potentials, and bizarre high-frequency repetitive discharges; positive for any of the myositis-specific autoantibodies; nondestructive arthritis or arthralgias; signs of systemic inflammation; or muscle biopsy findings compatible with inflammatory myositis. In addition, Dalakas MC & Hohlfeld developed their own diagnostic requirements. Due to the lack of consistent diagnostic criteria, PM is generally considered a disease of exclusion and is typically diagnosed when all other disorders are ruled out.

- The goals of treatment are to improve muscle strength and to avoid the development of extramuscular complications. Glucocorticoids are considered first-line therapy for PM. They are typically initiated with prednisone at a dose of 1 mg/kg per day, to a maximum daily dose of 80 mg. A steroid-sparing immunosuppressive agent, either methotrexate or azathioprine, is generally started along with glucocorticoid treatment so the patient can eventually begin to taper their steroids. Tapering of glucocorticoids is based on a combination of the improvement in muscle enzymes and recovery of muscle strength. Ideally, normalization of enzymes and complete recovery of muscle strength should occur before glucocorticoids are tapered. The initial response to glucocorticoids in the patient with PM typically takes four to six weeks for normalization of creatine kinase (CK) levels or three to four months to regain muscle strength.

- Some patients either relapse after an initial response or fail to respond to glucocorticoids and immunosuppressant therapy. These patients are considered to have recurrent or resistant disease. Multiple options exist as second-line therapy for those who do not respond adequately to glucocorticoids plus azathioprine or methotrexate. IVIG is considered the next step when the patient experiences recurrent or resistant disease. In PM, no controlled studies have been conducted, but IVIG has seems to be effective in approximately 70% of patients. Other therapies that have been shown to have some effectiveness either alone or in combination with other therapies include cyclosporin, mycophenolate mofetil, chlorambucil, and cyclophosphamide.

- Post-transfusion purpura

  - Post-transfusion purpura (PTP) is a rare but serious transfusion-associated complication characterized by thrombocytopenia developing within 2 weeks of transfusion accompanied by bleeding of variable severity that can be life-threatening. The prevalence of PTP is unknown and difficult to establish as the disease is difficult to differentiate from other thrombocytopenic conditions. According to case reports and series, previously pregnant women are the most commonly affected group with likelihood of developing PTP increasing with prior exposure to a specific human platelet antigen (HPA) absent on the patient's platelets. Subsequent transfusions re-expose recipients to the antigen triggering an immune response that induces platelet destruction. The most commonly implicated antibody is anti-HPA-1a made by patients with an HPA-1b/1b genotype.

  - PTP presents as severe thrombocytopenia with less than 10,000 platelets/μL sometimes accompanied by life-threatening bleeding with symptoms occurring 5 - 10 days after transfusion of blood products containing platelets (including whole blood, packed RBCs, platelets, and plasma). Bleeding is typically mucocutaneous (e.g. petechiae, epistaxis, gingival bleeding) with the most common sites of bleeding

being the mucous membranes, the gastrointestinal tract, and the urinary tract. PTP is considered a self-limited disease with recovery of platelet counts seen in approximately 20 days.

- Diagnosis of PTP can be challenging due to the wide array of thrombocytopenic syndromes with symptomatic overlap. Differential diagnosis includes immune thrombocytopenic purpura (ITP), drug-induced thrombocytopenia (DITP), thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), sepsis, and pseudo thrombocytopenia.

- Patients with acute, severe thrombocytopenia that develops approximately 5-10 days following a blood transfusion, together with primarily mucocutaneous bleeding and the presence of potent HPA-specific platelet antibodies, is diagnostic of PTP. Platelet antibody testing is required to confirm diagnosis. HPA genotyping may also be of additional benefit.

- Antibodies against HPA-1, HPA-2, HPA-3, HPA-4, HPA-5, and HPA-15 have been detected in the sera of patients with PTP. Direct and indirect antibody testing can be used to detect these platelet-specific antibodies; indirect methods test for antibodies in the patients plasma or serum while direct methods detect antibodies attached the patient's platelets. Direct testing can be limited in the presence of severe thrombocytopenia.

- Enzyme-linked immunosorbent assays (ELISA) are the most widely available technique for platelet antibody testing and can be used for both direct and indirect testing. Examples of platelet antibody assays that are widely used include the antigen capture ELISA (ACE), the modified antigen capture ELISA (MACE), the monoclonal antibody immobilization of platelet antigens (MAIPA) assay, and the platelet antibody bead array (PABA). Highly sensitive and specific antigen capture tests like the PABA or MAIPA assays should be performed since a strong HPA antibody is the hallmark of PTP. It is common for sera to contain platelet antibodies targeting multiple HPA even though HPA-1a antibodies are the most frequently detected in the serum of suspected PTP patients.

- HPA typing confirms HPA antibody specificity and guides clinical care for future transfusions. Two commonly used techniques include polymerase chain reaction using sequence-specific primers (PCR-SSP) and 5'exonuclease strategies. The typical result in PTP cases is the presence of HPA-1a antibodies in the patient's serum and an HPA-1b/1b (HPA-1a negative) genotype.

- The treatment of choice for PTP is intravenous immunoglobulin (IVIG) with recommended doses of 400 - 500 mg/kg/day for 1 - 10 days or 1 - 2 g/kg/day for 2 - 5 days. A favorable response to treatment is noted within as little as 2 days, with response rates of up to 90% having been reported. Corticosteroids may be given in addition to IVIG; however, the effectiveness of corticosteroids has not been proven. Platelet transfusions are generally ineffective at increasing platelet counts; however, they should be administered to patients with life-threatening bleeding. For cases refractory to IVIG or for more complex cases, whole blood or plasma exchange may be considered to quickly reduce the levels of autoantibodies.

  - Recurrence of PTP following subsequent transfusion is not common; however, previously affected patients who require transfusion should receive HPA-compatible blood products.

- Primary humoral immunodeficiency diseases

- Transient hypogammaglobulinemia of infancy (THI)

- Transient hypogammaglobulinemia of infancy is a type of primary immunodeficiency characterized by reduced IgG levels beginning at 5 to 24 months of age. Diagnosis of other common variable immunodeficiencies are not excludable until after this transient period. THI typically resolves at age 2 to 6 years old in the absence of diagnosis of another immunodeficiency disorder. While many patients remain asymptomatic, some experience recurrent infections such as upper and lower respiratory infections. Severe infections, including urinary tract infections, gastroenteritis, and invasive infections, may occur in severe cases. IVIG is recommended in THI patients with severe, life-threatening infections, or recurrent infections despite antibiotic therapy. Dosing of 400 mg/kg every 3 weeks has been effective in published studies

- X-linked agammaglobulinemia (congenital agammaglobulinemia)

  - X-linked agammaglobulinemia (congenital agammaglobulinemia) occurs in male infants, usually presenting in the first 3 years of life. Patients have either agammaglobulinemia or hypogammaglobulinemia, along with very low or absent CD19+ cells. Diagnosis is confirmed by molecular genetic testing for the BTK gene or protein expression. Lack of protein expression is considered when the patient has absent BTK mRNA on Northern blot analysis of neutrophils or monocytes or has absent BTK protein in monocytes or platelets. Probable diagnosis can also be made based off a family history of documented agammaglobulinemia or hypogammaglobulinemia. Diagnosis can also be confirmed when a patient has maternal cousins, uncles, or nephews with less than 2% CD19+ B-cells.

  - The most common clinical manifestations of this condition are bacterial infections, which can lead to sepsis, osteomyelitis, septic arthritis, and central nervous system infections. Patients are also susceptible to viral, fungal, and parasitic infections. Some patients may be diagnosed more proactively if there is a document history of the disease in the family. Median age of onset is 2.6 years in patients with a family history and 5.4 years in patients without a family history of the disease.

  - Immunoglobulin replacement therapy is the cornerstone of therapy in X-linked agammaglobulinemia. Observational studies show that it lowers morbidity and mortality in these patients. American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend lifelong immunoglobulin replacement therapy as both necessary and lifesaving. It must be used in combination with infection avoidance measures, vaccinations, and aggressive antibiotic therapy for infections. Recommended dosing for IVIG is 400 - 600 mg/kg every 3 - 4 weeks. Recommended dosing for subcutaneous IVIG is 100 - 200 mg/kg per week.

- Common variable immunodeficiency (CVID)

  - Common variable immunodeficiency is a heterogeneous primary immunodeficiency disorder affecting both children and adults. CVID comprises a group of hypogammaglobulinemia syndromes, stemming from multiple genetic defects, where patients have impaired B-cell differentiation and immunoglobulin production. Diagnosis is contingent on significantly reduced serum IgG levels, low levels of IgA and/or IgM, reduced response to immunizations, and exclusion of other immunodeficiency disorders.

  - Most patients experience chronic lung disease, autoimmune disorders, gastrointestinal disease, an increased susceptibility to lymphoma, and recurrent infections. Approximately 25% of patients have symptom onset during childhood or adolescence. Children, in particular, present with recurrent ear infections and concomitant autoimmune cytopenias and allergic disease. In severe cases, children present with failure to thrive.

  - IVIG has proven to reduce recurrent infections and complications in these patients. It is recommended for patients with significant impairments in immune globulin production, evidenced by approximately two standard deviations below the normal range for IgG and lack for response to protein and polysaccharide vaccines. IVIG with close monitoring may be considered in patients with less severe impairments in immune globulin production and minor responses to some vaccines. While the recommended maintenance dose is 400 mg/kg every 4 weeks, higher doses may be used in patients with recurrent major infections, chronic lung disease, enteropathy, and in pregnancy.

- Immunoglobulin subclass deficiency (e.g., X-Linked immunodeficiency with hyper-IgM)

  - Immunoglobulin subclass deficiency is a rare primary immunodeficiency diagnosed in adults and children with recurrent infections. Patients with immunoglobulin subclass deficiency have reduced serum concentrations of one or more subclasses of IgG, but normal total concentrations of IgG. Patients with laboratory findings of reduced subclasses of IgG, recurrent infections, and inadequate response to a vaccine challenge are considered to have clinically significant immunoglobulin subclass deficiency. Levels of IgG subclasses, including IgG1, IgG2, IgG3, or IgG4, should be confirmed on two occasions at least 2 - 4 weeks apart. Approximately 15% of patients also have an IgA deficiency. Many patients have concomitant asthma, chronic obstructive pulmonary disease (COPD), vasculitis, and cytopenias.

  - Like patients with other primary immunodeficiencies, these patients most often present with recurrent sinopulmonary infections. They require comprehensive treatment plans, including infection prevention precautions, along with management of COPD, asthma, and other conditions that would predispose them to infections. Aggressive antibiotic therapy and prophylaxis are recommended for patients with recurrent infections. Immunoglobulin replacement therapy is recommended in patients with recurrent infections not resolved with

prophylactic antibiotics. Evidence from retrospective studies have shown that IVIG treatment demonstrated reduced infections, decreases antibiotic use, and improved quality of life. American Academy of Allergy, Asthma, and Immunology 2016 guidelines state that IVIG may provide benefit in patients with isolated IgG subclass deficiency and recurrent infections. Recommended dosing is 400 - 600 mg/kg every 4 weeks.

- Combined immunodeficiency syndromes

  - Combined immunodeficiency syndromes include Wiskott-Aldrich syndrome, Severe Combined Immune Deficiency (SCID), DiGeorge Syndrome, and Ataxia Telangiectasia and are rare, inherited syndromes. These patients are prone to many opportunistic infections, and susceptibility often increases with age. Disease severity and degree of immunodeficiency is often dependent on the genetic defect. Patients with mild defects may not present with symptoms until early adulthood. SCID is often differentiated from other combined immunodeficiencies as a more severe condition with significant mortality as an infant due to infection.

- American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend immunoglobulin replacement therapy in patients with primary immune defects with absent B-cells, hypogammaglobulinemia, and impaired specific antibody production. Immunoglobulin replacement therapy is also FDA approved for the treatment of combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome and SCID. There are many combined immunodeficiencies, each with different molecular genetic defects. Please refer to clinical guidelines and literature to determine disease-specific diagnostic criteria and information about specific molecular genetic defects. Recommended dosing is usually 400 - 600 mg/kg every 4 weeks.

- Idiopathic hypogammaglobulinemia

- Hypogammaglobulinemia is a general term describing serum levels of IgG which are below the lower limits of normal. Diagnosis of a primary immunodeficiency is often retrospective and of exclusion. Patients with hypogammaglobulinemia should receive a comprehensive treatment plan, including infection prevention precautions, antibiotic prophylaxis, and adequate management of disease states that would predispose them to infections, including asthma and COPD. In patients with recurrent infections despite these measures, immunoglobulin replacement therapy is appropriate. American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend immunoglobulin replacement therapy in patients with hypogammaglobulinemia and impaired specific antibody production. Recommended dosing is usually 400 - 600 mg/kg every 4 weeks in these patients.

- Prophylactic post exposure for hepatitis A, measles (rubeola), varicella, and rubella in early pregnancy (GammaSTAN only)

- Human immune globulin (IG) is a blood product used to provide antibodies for short-term prevention of infectious diseases. GamaSTAN is the only intravenous immunoglobulin product approved for the use of post-exposure prophylaxis for Hepatitis A, measles, varicella, and rubella in early pregnancy. Its labeled indications are as follows:

- Prophylaxis following exposure to hepatitis A. It is not indicated in persons with clinical manifestations of hepatitis A or in those exposed more than 2 weeks previously.

- To prevent or modify measles in a susceptible person, one who has not been vaccinated and has not had measles previously, exposed fewer than 6 days previously. GamaSTAN is also indicated for pregnant women without evidence of immunity and may be especially indicated for susceptible household contacts of measles patients, particularly contacts under 1 year of age, for whom the risk of complications is highest.

- To modify varicella. Passive immunization against varicella in immunosuppressed patients is best accomplished by use of varicella zoster immune globulin (human). If unavailable, GamaSTAN, promptly given, may also modify varicella.

- To modify rubella in exposed women who will not consider a therapeutic abortion.

- Hepatitis A

    - IG provides protection against hepatitis A through passive transfer of antibody and has been shown to be 80 - 90% effective at preventing hepatitis A when administered within 2 weeks of exposure. Efficacy is greatest for post-exposure prophylaxis when IG is administered early in the incubation period. When administered later in the incubation period, IG might only attenuate the clinical expression of HAV infection.

    - According to the Advisory Committee on Immunization Practices (ACIP) recommendations for prevention of hepatitis A through active or passive immunization, people who have recently been exposed to Hepatitis A and have not been previously vaccinated should receive a single dose of IG as soon as possible within two weeks of exposure as efficacy when administered after 2 weeks has not been established.

    - If the hepatitis A vaccine is recommended for the person receiving IG, it may be administered simultaneously at a separate injection site.

- Measles (Rubeola)

- IG has historically been the blood product of choice for short-term measles prophylaxis and has been used as prophylaxis to prevent or attenuate measles disease since the 1940s, when it was demonstrated that IG can reduce the risk for measles or modify disease if administered within 6 days of exposure with a dose response effect.

- The ACIP recommends IG to prevent or modify measles in persons who are nonimmune within 6 days of exposure. It is not indicated for people who have received at least 1 dose of measles-containing vaccine at an age of greater than or equal to 12 months unless they are severely immunocompromised. Susceptible patient groups at risk for severe disease and complications from measles who should receive IG according to the ACIP recommendations include infants less than 12 months of age, pregnant women without evidence of measles immunity, and severely immunocompromised persons regardless of immunologic or vaccination status.

- Nonimmune patients 12 months of age or older who were exposed to measles and received GamaSTAN should also receive a measles vaccine, however, measles vaccine must be administered separately at least 5 months after GamaSTAN at which point the measles antibody titer will have disappeared.

- IG is not recommended to control measles outbreaks, but rather to reduce the risk for infection and complications in the person receiving it. IG has not been shown to prevent rubella or mumps infection after exposure and is not recommended for that purpose.

- Varicella

  - VariZIG®, a varicella zoster immune globulin preparation, is approved by the FDA and recommended by the ACIP for use as post-exposure prophylaxis of varicella in patients at high risk for severe disease who lack evidence of varicella immunity and for whom the vaccine is contraindicated. VariZIG is approved to be administered as soon as possible following varicella exposure, ideally within 96 hours for greatest effectiveness and after no more than 10 days. VariZIG is intended to reduce the severity of varicella. There is no convincing evidence that it will reduce the incidence of infection after exposure or modify established varicella infections. High risk groups for whom VariZIG is indicated include: immunocompromised children and adults, newborns of mothers with varicella shortly before or after delivery, premature infants, neonates and infants less than 1 year of age, adults without evidence of immunity, and pregnant women.

  - If VariZIG is unavailable, GamaSTAN may be given promptly to modify varicella post-exposure in immunosuppressed patients.

- Rubella

  - Rubella infection in pregnant women, especially during the first trimester, can result in miscarriages, stillbirths, and congenital rubella syndrome (CRS; an array of birth defects that often includes cataracts, hearing loss, mental retardation, and congenital heart defects). In addition, infants with CRS frequently exhibit both intrauterine and postnatal growth retardation. The risk for congenital infection and defects is highest during the first 12 weeks of gestation, and the risk for any defect decreases after the 12th week of gestation.

  - MMR vaccines should not be administered to women known to be pregnant or attempting to become pregnant. Additionally, post exposure MMR vaccination has not been shown to prevent or alter the clinical severity of rubella or mumps and is therefore not recommended for this purpose.

  - Some studies have suggested that the use of GamaSTAN in susceptible women post-rubella exposure can lessen the likelihood of infection and fetal damage. As such, GamaSTAN may be beneficial to modify rubella in pregnant women who will not consider a therapeutic abortion. GamaSTAN is not, however, recommended or approved for routine prophylaxis in early pregnancy in unexposed women.

- Pure red cell aplasia (PRCA)

- Pure red cell aplasia is a syndrome defined by a normocytic normochromic anemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow. Acquired PRCA may be either a primary disorder or secondary to some other disorder or agent. Primary acquired PRCA is an autoimmune disorder that is frequently antibody-mediated. Myelodysplastic syndromes may also present with the morphologic appearance of PRCA. Secondary acquired PRCA may be associated with collagen vascular or autoimmune disorders such as systemic lupus erythematosus; lymphoproliferative disorders such as chronic lymphocytic leukemia or large granular lymphocyte leukemia; infections, particularly parvovirus B19; thymoma and other solid tumors; or a variety of other disorders, drugs, or toxic agents.

- Diagnosis of PRCA is established when the patient meets all of the following: normocytic, normochromatic red blood cells; an absolute reticulocyte count less than 10,000/µL (less than 1% reticulocytes); normal white blood cell and platelet counts in the absence of a concurrent disorder such as CLL; less than 1% erythroblasts on bone marrow differential count; and no significant abnormalities in the myeloid, lymphocytic, or megakaryocyte lineages, unless the patient has a concurrent diagnosis of CLL or CML.

- Once a diagnosis is confirmed, the next step is to determine the cause which dictates the patient's treatment course. Testing should be done to distinguish between idiopathic, myelodysplastic, or secondary PRCA. All individuals who do not have CLL, CML, or myelodysplastic syndrome should have nucleic acid testing of peripheral blood for parvovirus B19 and treatment should not begin until those results are back.

If the patient is taking a drug known to cause PRCA, the drug should be discontinued immediately. All other possible secondary causes should be investigated as appropriate as well.

- For most causes of PRCA, immunosuppression is considered first-line therapy. However, if the patient is found to have PRCA due to parvovirus B19, IVIG is considered first-line therapy. IVIG contains antibodies against parvovirus and can reverse PRCA. Responses have been reported with doses as low as 400 mg/kg, although some have used the 2 g/kg dose divided over two to five days. While good response with IVIG is seen in patients with parvovirus B19, IVIG has not shown good efficacy in PRCA due to other causes.

  - Refractory Pemphigus Foliaceous

  - Pemphigus is a group of potentially life-threatening blistering disorders characterized by intraepithelial blisters in mucous membranes and skin that form due to a loss of keratinocyte adhesion. There are four major types: pemphigus vulgaris, pemphigus foliaceus, immunoglobulin A (IgA) pemphigus, and paraneoplastic pemphigus. Each form is distinguished by their own clinical features, autoantigens, and laboratory findings. Pemphigus vulgaris and pemphigus foliaceus are the two most common forms of pemphigus.

  - Pemphigus foliaceus is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis that results in the formation of superficial blisters. The most common sites of involvement include the scalp, face, and trunk. Skin lesions are typically small, scattered, superficial blisters that rapidly evolve into scaly and crusted erosions that can remain localized or converge to cover large areas of the skin. The Nikolsy sign, induction of skin blistering with manual pressure, is often present. Variants of pemphigus foliaceus include endemic pemphigus foliaceus, which presents similarly to the idiopathic form but is related to an environmental trigger, and pemphigus erythematosus, which describes pemphigus foliaceus localized to the malar region of the face. Pemphigus foliaceus may also be drug-induced with manifestations similar to idiopathic disease.

  - Assessing clinical, histologic, immunopathologic, and serologic findings is essential to proper diagnosis. Diagnosis requires clinical presentation and histopathology consistent with pemphigus foliaceus with either a positive DIF microscopy or serologic detection of autoantibodies against epithelial cell surface antigens. The following tests can confirm diagnosis of disease: lesional skin or mucosal biopsy for routine hematoxylin and eosin (H&E) staining; perilesional skin or mucosal biopsy for direct immunofluorescence (DIF); serum collection for enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence (IIF). All patients with pemphigus foliaceus have positive DIF results demonstrating intercellular deposition of IgG, though negative DIF studies may occur in patients with drug-induced pemphigus. IIF demonstrates intercellular deposits of IGG. Greater than 80% of patients with pemphigus foliaceus have circulating antibodies detectable by IIF. IIF cannot distinguish between pemphigus foliaceus and vulgaris. ELISA for IgG antibodies to desmoglein 1 and desmoglein 3 is more sensitive and specific than IIF for diagnosing pemphigus vulgaris and pemphigus foliaceus, with a sensitivity greater than 90%. Desmoglein 1 autoantibodies are found on ELISA for pemphigus foliaceus.

- Differential diagnosis includes seborrheic dermatitis, impetigo, subacute cutaneous lupus erythematosus, IgA pemphigus, and the non-IgA pemphigus form of subcorneal pustular dermatosis.

- Pemphigus foliaceus is associated with the potential for severe morbidity and mortality therefore, treatment is indicated at the time of disease onset regardless of presenting disease severity. The goal of treatment is to induce complete remission while minimizing treatment-related adverse effects.

- An international consensus of experts supports the use of systemic glucocorticoids as first-line therapy for pemphigus foliaceus. Systemic glucocorticoids are typically given to attain rapid disease control with clinically significant improvement seen within 2 - 3 weeks. Their use is supported by randomized trials and studies documenting improvement in pemphigus with glucocorticoid monotherapy as well as extensive clinical experience. Oral therapy with prednisone, methylprednisolone, or prednisolone is the most common mode of administration at 0.5 to 1.5 mg/kg/day of prednisone or prednisolone, though higher doses can also be used. Full disease control requires 6 - 8 weeks. Tapering should begin once disease activity is under control with a goal of reaching the lowest dose needed to keep the disease controlled.

    - Immunomodulators are used adjunctively to minimize glucocorticoid consumption and reduce the risk of adverse effects of long-term and high-dose glucocorticoid therapy. They can be used at the onset of therapy particularly in cases of increased risk with corticosteroid therapy, complications due to prolonged use, or dose dependency above 10 mg/day of prednisone. First-line corticosteroid-sparing immunomodulator agents according to an international consensus of experts include azathioprine and mycophenolate mofetil. Adjuvant therapy is maintained until oral glucocorticoids have been completely discontinued and dose reduction begins 8 weeks after discontinuation of glucocorticoids. There is limited evidence that adding adjuvants is superior to corticosteroid monotherapy. Evidence has shown that the primary benefit of adjuvant therapy is in its glucocorticoid-sparing effect rather than a disease-modifying effect.

- Rituximab may also be used as a first-line treatment in new-onset moderate-to-severe pemphigus along with prednisone to allow for reduced prednisone doses, lower rates of corticosteroid-induced side effects, and more rapid corticosteroid tapering. A limiting factor to this regimen for initial treatment, however, is the high cost of rituximab.

- Disease activity is considered under control after a period of weeks during which no new lesions form, the Nikolsy sign is no longer present, and the majority of lesions have healed. Therapy at this point should be slowly reduced to the lowest dose required to prevent new lesions from appearing. Glucocorticoids are tapered first followed by a gradual reduction of non-steroidal adjuvant.

- Patients with refractory pemphigus foliaceus unresponsive to traditional first-line treatment may benefit from rituximab, IVIG, immunoadsorption, plasmapheresis, or cyclophosphamide. There is a lack of robust, high-quality literature on the treatment of

refractory pemphigus in addition to a lack of definitive guidelines on how to best approach refractory treatment. Choice of treatment is influenced by patient tolerability, treatment availability, and treatment-specific contraindications.

- IVIG in refractory pemphigus foliaceus is typically combined with systemic corticosteroids initially and immunomodulator adjuvants. The recommended dose of IVIG for refractory pemphigus foliaceus is 2 g/kg over 2 to 5 days per month.

- Solid organ transplant

- Patients at high risk for antibody mediated rejection (AMR) includes but is not limited to highly sensitized patients based on panel reactive antibody evaluation, those receiving an ABO incompatible organ, specific characteristics of donor-specific antibodies such as type and strength. AMR can occur after transplant, most commonly within 6 months.

- Pre-treatment with IVIG (desensitization) has been shown to reduce the risk of AMR in highly sensitized solid organ transplant patients. The goal of therapy is early antibody elimination with IVIG, pheresis, or a combination of modalities. A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant. The usual dose of IVIG is 2 g/kg every 4 weeks.

- Stiff Person Syndrome

  - Stiff-person syndrome (SPS, also referred to as stiff-man syndrome) is a rare disorder involving progressive muscle stiffness, rigidity, and spasm involving the axial muscles that results in severely impaired ambulation. Women are affected two to three times more often than men with the average age of presentation between 20 and 50 years. SPS is often associated with type 1 diabetes mellitus and other autoimmune disorders.

  - The three major types of SPS include Classic SPS, partial SPS, and paraneoplastic SPS. Classic SPS accounts for 70 - 80% of SPS patients; characteristics of classic SPS include truncal stiffness, generalized rigidity, and frequent muscle spasms, all of which result in a wide-based, awkward gait. The clinical hallmark of SPS is an extreme degree of muscle stiffness and rigidity. Partial SPS accounts for 10 - 15% of SPS patients, the most common form being stiff-limb syndrome where patients present with difficulty ambulating due to stiffness and lack of mobility affecting one limb (typically the leg) while sparing the trunk. Paraneoplastic SPS is extremely rare and seen in less than 2% of SPS patients. Clinically, paraneoplastic SPS is indistinguishable from classic SPS; however, paraneoplastic SPS patients are usually glutamic acid decarboxylase (GAD) antibody-negative and often have concurrent features of an underlying neoplasm. Malignancies associated with SPS include breast cancer, lung cancer, and Hodgkin lymphoma. Remission of neurologic symptoms has been noted after excision of the tumor and subsequent glucocorticoid treatment.

- There are no formally accepted criteria for diagnosing SPS. Muscle hardening to a board-like sensation is probably the most specific clinical observation establishing diagnosis. The presence of the following is generally considered necessary for diagnosis: stiffness in axial and limb muscles resulting in impaired ambulation; presence of superimposed episodic spasms precipitated by sudden movement, noise, or emotional upset; a positive therapeutic response to oral diazepam or findings of continuous motor-unit activity on electromyography (EMG) are abolished by IV diazepam; and absence of other neurologic disorders that could explain the clinical features.

- Diagnostic evaluation may include:

  - Anti-glutamic acid decarboxylase (GAD) antibody testing, which is positive in approximately 2/3 of patients. If present, anti-GAD antibodies support diagnosis; however, they may be absent.

  - A therapeutic trial of diazepam starting at 5 mg orally four times daily and slowly titrating up to the max dose required for symptom control without excessive sedation.

  - EMG testing including to evaluate response to oral diazepam

- In patients with characteristic clinical findings, anti-GAD antibodies, and a positive response to diazepam, diagnosis can be made without an EMG. The pain and stiffness characteristic of SPS, however, may mimic other conditions including ankylosing spondylitis, Parkinson disease, tetanus, axial dystonia, and focal limb or joint disorders. Alternative diagnoses must be ruled out.

- Treatment of SPS is directed at controlling symptoms to improve mobility and function. Benzodiazepines are considered the ideal initial symptomatic treatment for SPS with either diazepam 20 - 80 mg/day in three to four divided doses or clonazepam 10 - 30 mg orally two to four times daily. Diazepam daily doses to control disease may be as high as 100 – 200 mg/day while clonazepam can reach a maximum of 24 – 32 mg/day.

- In patients intolerant to high doses of benzodiazepines or with an unsatisfactory response, clinical experience supports the use of baclofen beginning at 10 mg 2 - 3 times daily with a gradual upward titration to a maximum of 80 mg daily in divided doses. Baclofen can be used as monotherapy or in conjunction to benzodiazepine therapy depending on the extent of benefit achieved from the maximally tolerated benzodiazepine. The use of baclofen is supported by clinical experience thought it has not been tested in randomized trials.

- For patients with continued inadequate symptomatic relief and in patients with severe disease where symptoms continue to significantly interfere with activities of daily living, the use of immune modulating therapy is recommended. IVIG is generally initiated in patients lacking symptomatic relief after the use of benzodiazepines and/or baclofen, corresponding to the European Federation of Neurological

Societies (EFNS) 2008 guidelines for the use of IVIG in the treatment of neurological diseases. IVIG is administered initially at 2 g/kg given in a treatment course over 2 - 3 infusions, each usually separated by 3 - 5 days. If the first round of IVIG does not produce a significant change in function, a second round can be tried with dosing of 2 g/kg per infusion given every 2 weeks for up to 4 doses.

- Additional therapies that may be beneficial for SPS based on findings from case reports and small uncontrolled series include corticosteroids, azathioprine, levetiracetam, valproic acid, gabapentin, plasma exchange, and rituximab/rituximab biosimilars.

- Systemic Lupus Erythematous (SLE)

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect virtually any organ in the body. SLE is a clinically heterogenous disease with patients presenting with variable clinical manifestations that range from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. The diagnosis is generally based on clinical grounds in the presence of characteristic serological or laboratory abnormalities after having excluded alternative diagnoses. A prominent feature of disease is the production of antinuclear antibodies (ANA). Constitutional symptoms, such as, fatigue, fever, and weight loss, are typically present in most SLE patients at some point during the disease course with fatigue being the most common complaint. Arthritis and arthralgias occur in over 90% of SLE patients and often present as one of the earliest manifestations of disease. Mucocutaneous, cardiac, renal, gastrointestinal, pulmonary, neuropsychiatric, hematologic, and ophthalmologic involvement may also occur.

- The goals of SLE therapy are to ensure long-term survival, have the lowest possible disease activity, prevent organ damage, minimize drug-related toxicities, and improve quality of life. Treatment is individualized based on the clinical manifestations, disease activity and severity, and patient comorbidities.

- Treatment in SLE should aim at remission or low disease activity and prevention of flares in all organs while maintained on the lowest possible dose of steroids. SLE flares can be treated according to the severity of organ involvement via adjusting current ongoing therapies to higher doses, switching medications, or adding new therapies. Treatment of organ or life-threatening SLE includes an initial treatment with high-intensity immunosuppressive therapy to control disease activity followed by less intensive long-term therapy to consolidate the response and prevent relapse.

- According to the 2019 update of the EULAR recommendations for the management of SLE, hydroxychloroquine is recommended for all patients with SLE unless contraindicated. Glucocorticoids can provide rapid symptom relief and may be used with hydroxychloroquine. The dose and route of administration of glucocorticoids are dependent on the type and severity of organ involvement. Immunosuppressive therapies such as methotrexate, azathioprine, and mycophenolate should be considered if a patient is not responding to hydroxychloroquine with or without glucocorticoids or is unable to reduce glucocorticoid doses to under 7.5 mg/day for chronic use. They can also be included as initial therapy for organ-threatening disease. Cyclophosphamide is another

immunosuppressant option, however, it's recommended only to be used for severe organ threatening or life-threatening SLE or as rescue therapy for patients unresponsive to other immunosuppressants.

- Hematologic manifestations of SLE frequently requiring treatment include thrombocytopenia and autoimmune hemolytic anemia (AIHA). The 2019 EULAR recommendations suggest first-line treatment of significant lupus thrombocytopenia, platelets less than 30,000/mm^3, with high dose glucocorticoids in combination with an immunosuppressant, such as, azathioprine, mycophenolate mofetil, or cyclosporine. The role of the immunosuppressant is primarily for maintenance of response after acute treatment and as a glucocorticoid-sparing agent. IVIG may be considered in the acute phase after an inadequate response to high-dose glucocorticoids or to avoid glucocorticoid-related complications. The recommended dose of IVIG per the guidelines is 1 g/kg/day for 1 - 2 days. Refractory cases may be treated with rituximab/rituximab biosimilar or cyclophosphamide.

- The use of IVIG in SLE outside of significant lupus thrombocytopenia is not recommended by or addressed in the 2019 EULAR guidelines. Some small case reports and series have shown some benefit of IVIG in cutaneous lupus erythematosus, central nervous system lupus, and lupus myocarditis, however, there is a paucity of robust data or literature definitively supporting the clinical efficacy and use of IVIG for these and other manifestations of SLE.

- There are multiple IVIG treatment options. There an no clinical trials comparing the efficacy of one therapy to another. Choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability.

- Immune globulin replacement therapy is indicated for many labeled and off-label indications and is traditionally dosed using a patient's actual body weight. IVIG and SCIG products have insignificant distribution into fat tissue and are only present in the intravascular space and extracellular fluids. Clinical literature supports alternative dosing strategies that provide comparable drug exposure without altering the clinical outcomes of treatment. Therefore, pateints should be dosed using adjusted body weight in situations where the pateint's dody mass index is 30 kg/m^2 or greater or their actual body weight is 20% to 30% higher than their ideal body weight.

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Policy History		
#	Date	Change Description
2.0	Effective Date: 12/04/2025	Updated to include Qivigy and criteria for drug induced secondary hypogammaglobulinemia
1.9	Effective Date: 08/07/2025	Updated to include Gammagard Liquid ERC
1.8	Effective Date: 08/08/2024	Updated to add Yimmugo, remove the statement requiring subcutaneous products only be allowed for the FDA approved indication, and require immunoglobulin not be used in combination with biologic therapies for CIDP
1.7	Effective Date: 06/06/2024	Annual review of criteria, no changes were made to the criteria.
1.6	Effective Date:	Annual review of criteria was performed, no changes were made

	04/11/2024	Background was updated to include information regarding IVIG in PANDAS
1.5	Effective Date: 02/08/2024	Updated to add Flebogamma DIF and Alyglo
1.4	Effective Date: 06/08/2023	Updated Inflammatory demyelinating polyneuropathy (acute) criteria due to Medical director's feedback to require lumbar puncture and if non-confirmotory, then require EMG/NCS or an MRI
1.3	Effective Date: 04/06/2023	Updated to allow approval for no less than 60 days for any indication
1.2	Effective Date: 10/06/2022	Updated to not allow use of IVIG with any other biologic therapy for myasthenia gravis
1.1	Effective Date: 02/10/2022	Annual review of criteria was performed, no changes were made
1.0	Initial Effective Date: 01/01/2021	New Policy

Infliximab Policy
Avsola™ (infliximab-axxq) Q5121
Inflectra® (infliximab-dyyb) Q5103
Ixifi™ (infliximab-qbtx) Q5109
Infliximab (Remicade) J1745
Infliximab-abda J3590
Renflexis® (infliximab-abda) Q5104
Zymfentra® (infliximab-dyyb) J1748

Background Information:

- Infliximab is a tumor necrosis factor inhibitor (TNFi) approved for the following indications:
  - Induction and maintenance treatment of adults and pediatric patients 6 years of age and older with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy
  - Adults with fistulizing CD
  - Induction and maintenance treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy
  - Induction and maintenance treatment of pediatric patients 6 years of age and older with moderately to severely active UC who have had an inadequate response to conventional therapy
  - Treatment of adults with moderately to severely active rheumatoid arthritis (RA) when used in combination with methotrexate
  - Adults with active ankylosing spondylitis (AS)
  - Adults with psoriatic arthritis (PsA)
  - Treatment of adults with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate

- Remicade by Janssen was the first infliximab product approved by the FDA. Since its introduction to market, four infliximab biosimilar products have also been approved: Inflectra, Renflexis, Avsola and Ixifi. In addition, Janssen released an "unbranded" formulation of infliximab in November 2021. This "unbranded biologic" is not a biosimilar but rather the same drug re-labeled, similar to authorized generics for non-biologics.

- There is a large body of literature, punctuated by the NOR-SWITCH trial, evaluating the impact of switching from reference infliximab (Remicade) to a biosimilar. The great majority of studies do not report differences in safety, efficacy, or immunogenicity after a single switch. Data suggests a low risk of safety concerns or loss of efficacy after switching to biosimilar infliximab. There are no studies showing that if a biosimilar does not work, a patient will respond to the innovator product or another biosimilar.

- There is insufficient information regarding the concurrent use of infliximab products with other biologic agents or targeted DMARDs. Due to the lack of robust clinical evidence and the possibility of an increased risk of infection, infliximab products are not recommended for use in combination with other biologics or targeted DMARDs.

- Crohn's Disease

- The 2018 American College of Gastroenterology (ACG) guidelines establish therapeutic recommendations for patients with Crohn's disease based upon disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Current therapeutic approaches should be considered a sequential continuum to treat acute disease or induce clinical remission and then to maintain response/remission. In general, clinical evidence of improvement should be evident within 2 – 4 weeks and the maximal improvement should occur within 12 – 16 weeks. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease, have their medication dose adjusted in order to attempt to optimize therapy, or advance to treatment for moderate to severe disease according to their clinical status.

- Corticosteroids are used primarily for the treatment of CD flares. Conventional corticosteroids are effective for reducing the signs and symptoms of active CD and induction of remission in patients with moderately to severely active CD. Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active disease. The ACG guidelines recommend prednisone equivalent doses ranging from 40 to 60 mg per day. These doses are typically maintained for 1 –2 weeks and tapered at 5 mg weekly until 20 mg and then 2.5 –5 mg weekly. Once begun, care should be taken to ensure that corticosteroids are successfully discontinued, and steroid-sparing agents should be used.

- In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, mercaptopurine, azathioprine, and intramuscular or subcutaneous methotrexate are effective as steroid-sparing agents and are recommended by the guidelines. Maximum effectiveness of these agents can be seen between 8 to 12 weeks from therapy initiation. Methotrexate is also

recommended in combination with steroids as effective for treatment of moderately active steroid-dependent/resistant CD. Cyclosporine, tacrolimus, and mycophenolate are not recommended for treatment of CD.

- TNFi biologics including infliximab, adalimumab, and certolizumab pegol are effective for treatment of patients with CD who inadequately respond to treatment with corticosteroids, thiopurines, and methotrexate. These agents are rapid in onset of effect, with benefit often noted within 2 weeks of initiating therapy. Treatment guidelines do not recommend the use of one agent over another. The ACG guidelines also recommend the use of biologics in combination with immunosuppressants to help decrease the formation of antibodies against the biologic therapy. There are no robust, published studies to support use of biologic agents in combination.

- The 2021 American Gastroenterological Association (AGA) guidelines include similar recommendations for the management of moderate-to-severe CD compared to the recommendations cited in the 2018 ACG guidelines. Both guidelines recommend corticosteroids over no treatment for induction of remission. Additionally, both guidelines recommend thiopurines, such as azathioprine or 6-mercaptopurine, as steroid-sparing agents for maintenance of remission. The AGA guidelines also recommend the same biologic agents cited in the ACG guidelines for treatment of CD, with the exception of Tysabri® (natalizumab), which the ACG suggests against use of due to its associated risk of progressive multifocal leukoencephalopathy (PML).

- Of note, the AGA guidelines conditionally recommend earlier introduction of biologic therapy prior to failure of corticosteroids; however, this recommendation is supported by a low level of clincial evidence. To date, no blinded randomized controlled trials (RCTs) have demonstrated the superiority of early introduction of biologic therapy compared to conventional induction therapy with corticosteroids followed by steroid-sparing therapy. The 2021 AGA guideline authors also acknowledge that earlier therapy with either combination immunomodulotor plus biologic therapy or biologic monotherapy may result in over-treating some patients and potentially exposing them to treatment-related risks and costs with limited benefit.

- Ulcerative Colitis

- The 2019 American College of Gastroenterology guidelines and the 2020 American Gastroenterology Association guidelines state therapeutic management in ulcerative colitis should be guided by the specific diagnosis, an assessment of disease activity, and disease prognosis. Treatment selection should be based not only on inflammatory activity but also on disease prognosis.

- Remission can be induced using a variety of medications, including, oral 5-aminosalicylates (5-ASA), corticosteroids, or biologic agents. In patients with mild to moderately active disease, treatment with 5-ASA therapy has proven to be safe and efficacious for induction. Recommended dosing is 2 grams per day of oral 5-ASA or at least 1 gram per day of rectal 5-ASA with improvement usually seen within 4 weeks. A typical treatment course may last up to 8 weeks.

- Oral steroids are recommended for induction for patients with severe disease or those who did not respond to 5-ASA therapy. The typical starting doses of oral prednisone are 40 – 60 mg per day, and clinical response is expected within 5 – 7 days of treatment. A typical treatment course with oral prednisone is 14 days. The duration of systemic corticosteroids should be as short as possible with early initiation of steroid-sparing therapy. The speed of the taper should be guided by clinical symptoms, cumulative steroid exposure, and onset of action of alternate therapies. Those unable to taper off of 10-20 mg of prednisone per day without relapsing are considered steroid dependent. Use systemic corticosteroids for maintenance of remission is not recommended.

- Thiopurines, such as azathioprine and mercaptopurine, can be used to maintain remission. Thiopurines are slow acting with their maximum effectiveness seen between 8 to 12 weeks from therapy initiation. They do not induce remission in moderately to severely active ulcerative colitis. Similarly, methotrexate is not an effective induction agent for induction or maintenance of remission.

- In patients with moderate to severe disease, TNFi, Entyvio® (vedolizumab), and Stelara® (ustekinumab) may be recommended for the induction and maintenance of remission. For patients with moderate to severe disease in remission, guidelines do not recommend biologic monotherapy over thiopurine monotherapy. Thiopurines can be used as adjunctive therapy for reducing immunogenicity against biologic therapy and are guideline recommended.

- TNFi (infliximab, adalimumab, and golimumab) are effective for treatment of patients with ulcerative colitis. These agents are rapid in onset of effect, with benefit often noted within 2 weeks of initiating therapy. Treatment guidelines do not recommend the use of one agent over another as there have been no head-to-head trials comparing the agents. For patients who had an initial response to aTNFi but lost efficacy, it is recommended that patients switch to an alternative TNFi therapy. For patients who are primary non-responders to therapy with a TNFi, it is recommended to consider an agent with a different mechanism.

- Rheumatoid Arthritis

- The 2021 American College of Rheumatology (ACR) Guidelines for the Treatment of Rheumatoid Arthritis (RA) established recommendations for the care of adult RA patients. The guidelines state that treatment decisions should follow a shared decision-making process and should be reevaluated within a minimum of 3 months based on the efficacy and tolerability of the DMARD(s) chosen.

- For the initial treatment of symptomatic RA, the guidelines strongly recommend the use of conventional synthetic DMARD (csDMARD) monotherapy in those who are DMARD-naive. csDMARD monotherapy is a less costly first line treatment option with an extensive safety record accompanied by well-documented clinical efficacy and a large body of clinical experience and familiarity among prescribers. csDMARDs in the guidelines refer to methotrexate (MTX), hydroxychloroquine, leflunomide (LEF), and sulfasalazine. Azathioprine, cyclosporine, minocycline, and gold were not included due to their infrequent use in RA and lack of new data since the prior guidelines were published. Oral MTX is

recommended as the preferred initial DMARD for patients with moderate-to-high disease activity, and hydroxychloroquine is recommended as the preferred initial DMARD for patients with low disease activity.

- If disease activity remains moderate or high despite optimal dosing of methotrexate monotherapy, the use of dual therapy with methotrexate plus biologic DMARD (bDMARD; etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, sarilumab, rituximab) or targeted synthetic DMARD (tsDMARD; tofacitinib, baricitinib, upadacitinib) therapy is conditionally recommended over the use of triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine). The guidelines do not inform preference of bDMARD over tsDMARD therapy (or vice-versa) for use in combination with MTX. No one agent has been shown to be superior to another. The guidelines do acknowledge the emergence of safety signals for the JAK inhibitor class (tsDMARD), and state that further modification of this recommendation may be necessary as additional data are published.

- A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a pre-defined target (low disease activity or remission).

- Ankylosing Spondylitis

- Axial spondyloarthritis, comprising ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (NRAS), is the main form of chronic inflammatory arthritis affecting the axial skeleton. Non-radiographic means that damage to the joints is not visible on X-ray. When changes to the vertebrae (the bones of the spine) or sacroiliac joints don't show any changes on an X-ray, that's known as NRAS. Once the joints are clearly affected on an X-ray, a person can be diagnosed with AS.

- The 2019 American College of Rheumatology recommendations for AS and NRAS are similar. In adult patients who have active disease despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDS), treatment with TNFi are recommended. They do not recommend any particular TNFi as the preferred choice for the typical patient. Secukinumab or ixekizumab is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi, whereas for patients with a secondary nonresponse (i.e. those who relapse after an initial response) it may be beneficial to switch to a different TNFi rather than immediately switch to a different biologic class. In the case of nonresponse (primary or secondary), the guidelines recommend against switching to treatment with a biosimilar since clinical response would not be expected to be different.

- Psoriasis

- Psoriasis is a chronic, painful and life-altering immune-mediated disease which predominantly manifests with skin and joint involvement. Patients may also experience significant cardiovascular and psychological comorbidities. Approximately 2% of U.S. adults are affected by

psoriasis (men and women equally), and it can occur at any age. Approximately 90% of psoriasis-affected patients have plaque psoriasis, which is characterized by well-defined round or oval plaques that vary in size and often coalesce. The severity of psoriasis is defined as: mild = less than 3% of body affected; moderate = 3-10% of body affected; and severe being more than 10% of the body affected.

- Per the 2020 Joint American Academy of Dermatology (AAD) - National Psoriasis Foundation (NPF) guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures: topical corticosteroids provide a high efficacy and good safety option for patients with localized disease. They are generally recommended as first-line therapy. Choice of steroid potency may depend on severity, location, patient preference, and patient age, while the duration of treatment may vary with steroid potency, location and severity of disease often ranging from 2-12 weeks. Therapeutic regimens may include 2-4 weeks with a topical steroid applied twice daily, followed by a maintenance regimen where topical steroids are alternated with a steroid-sparing topical agent. Treatment with topical steroids for over 12 weeks is recommended under careful supervision by a physician.

- Per the 2019 Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with phototherapy: phototherapy serves as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications or simply seeking an adjunct to a failing regimen. Guidelines also state that the majority of patients with mild-to-moderate disease have adequate disease control with topical therapies and phototherapy alone.

- Per the 2020 Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with systemic nonbiologic therapies: many oral medications, including methotrexate, cyclosporine, and acitretin, have been used for decades to treat psoriasis, each with its own benefits and risks. Most work by targeting the immune system, whereas others, such as acitretin, work predominantly by decreasing keratinocyte hyperproliferation, thus restoring the normal epidermal differentiation. Both methotrexate and cyclosporine are category A guideline recommendations for the treatment of moderate to severe psoriasis in adults and for severe, recalcitrant psoriasis, respectively. Studies examining the use of methotrexate and cyclosporine in psoriasis showed the primary efficacy endpoints met within 12-16 weeks. Acitretin is a category B guideline recommendation as monotherapy for plaque psoriasis, with full treatment response expected within 3-6 months.

- Per the 2019 Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics: biologic agents, as monotherapy or combined with other topical or systemic medications, have a high benefit-to-risk ration. TNFi, interleukin-12/23 inhibitor (IL-12/IL-23i), IL-23i, and IL-17i biologics have a category "A" recommendation as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis. TNFi biosimilars approved by the FDA should be considered similar to the reference branded version of the drug and therefore interchangeable. Guidelines do not recommend one product over another and note the similar efficacy seen across biologics within the same class.

  - Psoriatic Arthritis

- Psoriatic Arthritis (PsA) is a chronic inflammatory disease often associated with psoriasis. PsA occurs in up to 30% of patients with psoriasis, most commonly appearing between the ages of 30 and 50, and causes pain, stiffness, and swelling in and around the joints. If not properly treated, progressive joint damage may occur.

- Per the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guideline for the treatment of psoriatic arthritis: all recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.

- In treatment-naïve patients, oral systemic medications (OSMs), such as methotrexate, sulfasalazine, cyclosporine, and leflunomide, may be used in patients without severe psoriatic arthritis and without severe psoriasis. OSMs have robust longitudinal safety and efficacy data in patients with PsA. Maximal response to OSMs are most commonly achieved within 3 months of therapy.

- If PsA remains active despite OSM therapy, switching to a TNFi, an IL-17i, or an IL-12/23i biologic is recommended over switching to a different OSM; switching to a TNFi biologic over an IL-17i or IL-12/23i biologic is conditionally recommended in this scenario based on moderate quality evidence. The detailed recommendations for subsequent therapies can be found in the 2018 ACR/NPF guideline for the treatment of psoriatic arthritis.

  - Generalized Pustular Psoriasis

- Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening neutrophilic skin disease characterized by flares consisting of widespread eruptions of painful, sterile pustules. Patients with acute GPP may appear systemically ill and require hospital admission for adequate supportive care, and flares can be so disruptive to the system that they can trigger sepsis, cardiovascular complications, and renal failure. Flare frequency varies among patients and may be spontaneous or triggered by stress, infection, medication, or pregnancy. The clinical course of GPP varies and can be relapsing with recurrent flares or persistent with intermittent flares.

- The European Rare and Severe Psoriasis Expert Network (ERASPEN) consensus statement on phenotypes of pustular psoriasis (2017) define GPP as macroscopically visible primary sterile pustules occurring on non-acral skin and not within psoriasis plaques. GPP may occur with or without systemic inflammation and with or without psoriasis vulgaris and should only be diagnosed when the condition has relapsed at least once or when it persists for more than 3 months.

- The goals of treatment of GPP are to improve skin manifestations, alleviate systemic symptoms, and minimize the risk for life-threatening systemic complications. There are no standard US or international guidelines for the treatment of GPP as high-quality data on the efficacy of treatments is lacking. Japanese guidelines for the treatment of GPP (2018) and the National Psoriasis Foundation (NPF) Medical Board (2012) recommend an oral retinoid (e.g. acitretin), cyclosporine, methotrexate, and various biologics as potential systemic treatments for GPP. In the United States, these therapies are used off-label to treat GPP flares, and the choice of systemic agent is based on disease severity.

Demonstration of efficacy with any of these agents is solely based on limited evidence from case reports and small, uncontrolled trials. No randomized controlled trials or other comparative studies have been done comparing treatment methods.

- Infliximab has a long history of off-label use in GPP and use is supported by the NPF Medical Board and the Japanese guidelines. It is often used for more severe disease as marked improvement can be seen within the first few days of treatment. Japanese guidelines cite the effects of infliximab as apparent within 24-48 hours in many cases and a clear effect often seen after 1 to 3 administrations. Once the flare has resolved, patients can be transitioned to alternative therapies like methotrexate or a retinoid or remain on infliximab for maintenance.

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Policy History		
#	Date	Change Description
1.9	Effective Date: 12/04/2025	Added unbranded Renflexis product – Infliximab-abda – to the policy
1.8	Effective Date: 10/09/2025	Annual review of criteria performed, no changes were made
1.7	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.6	Effective Date: 12/14/2023	Updated to add FDA approved indications
1.5	Effective Date: 10/12/2023	Annual review of criteria performed, no changes were made
1.4	Effective Date: 10/06/2022	Added criteria for generalized pustular psoriasis
1.3	Effective Date: 12/09/2021	Removed FDA approved indication, phototherapy and oral DMARD criteria for psoriasis, and the oral DMARD criteria for psoriatic arthritis, and added trial of one topical corticosteroid for psoriasis indication.
1.2	Effective Date: 08/12/2021	Removal of criteria requiring documented negative TB test
1.1	Effective Date: 02/04/2021	Removal of the topical steroid criteria for psoriasis indication
1.0	Effective Date: 01/01/2021	New Policy

Intravenous Iron Replacement
Feraheme® (ferumoxytol) Q0138 / Q0139
Generic Ferrlect® (sodium ferric gluconate complex) J2916
INFeD (iron dextran) J1750
Injectafer® (ferric carboxymaltose) J1439
Monoferric® (ferric derisomaltose) J1437
Triferic®**/Triferic AVNU**® (ferric pyrophosphate citrate) J1445
Venofer® (iron sucrose) J1756

Background Information:

- The most common causes of iron deficiency anemia are decreased dietary intake, reduced absorption, and blood loss. In resource-rich countries such as the United States, the major cause of iron deficiency is blood loss, either overt or occult. Overt bleeding is usually caused by trauma, hematemesis or melena, hemoptysis, menorrhagia, pregnancy and delivery, or hematuria. Occult bleeding is usually caused by gastrointestinal conditions, such as, gastritis, malignancy, or telangiectasia or hemolysis with urinary losses. The most common symptoms of anemia are fatigue, weakness, headache, irritability, exercise intolerance, shortness of breath on exertion, vertigo, and angina. Diagnosis of iron deficiency anemia is made by low hemoglobin and hematocrit levels and serum ferritin level. Serum ferritin is the key indicator of iron stores in otherwise healthy adults.

- The treatment for iron deficiency anemia is iron replacement, usually with oral over-the-counter (OTC) iron preparations or via intravenous iron. In the presence of functioning erythropoiesis, iron supplementation is adequate to replenish iron stores and restore blood loss. However, due to the gastrointestinal adverse effects of oral iron as well as absorption issues, intravenous iron may be preferable.

- There are currently multiple intravenous iron therapies on the market. Neither the 2012 Kidney Disease: Improving Global Outcomes (KDIGO clinical practice guideline for anemia in chronic kidney disease or the 2025 National Comprehensive Cancer Network hematopoietic growth factors treatment guidelines recommend one intravenous product over another. All have similar efficacy and there is no head to head data showing superiority of one product over the other. Choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 08/10/2023	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 07/01/2023	New Policy

Izervay™ (avacincaptad pegol)
HCPCS: J2782

Background Information:

- Geographic atrophy is an advanced and severe form of dry age-related macular degeneration (AMD). It is caused by the gradual breakdown of light-sensitive cells in the macula resulting in the growth of irreversible lesions in the retinal pigment epithelium (RPE). GA progression causes a gradual loss of visual function. Symptoms include scotomas, difficulty recognizing faces, decreased reading speed, impaired dark adaptation, low luminance deficit (LLD), impaired contrast sensitivity, and difficulty driving at night. More than half of all patients with GA will experience significant impairment of everyday vision, and about 20% of patients will develop severe vision loss with visual acuity of 20/200 or worse.

- The exact cause of GA is unknown but it is thought the disease is the result of a multifactorial process. The most significant risk factors include age and family history with genetics playing a role in disease development. It is thought errors found in the genes of the complement cascade may cause inflammation making the eye more susceptible to GA. Smoking and a higher body mass index are also risk factors.

- Diagnosis is made by an ophthalmologist during a dilated exam and/or with retinal imaging. In a dilated exam, geographic atrophy appears as a patch of retina that's missing its dark melanin pigment. Imaging techniques including retinal color photographs, optical coherence tomography (OCT), or autofluorescence photographs can also be used to detect GA.

- Izervay is a C5 complement inhibitor indicated for the treatment of GA secondary to AMD. It targets the complement overactivation generating GA progression preventing lesion growth and reducing the likelihood of severe disease.

- GA can be secondary to other conditions outside of AMD. Those include Stargardt disease, cone rod dystrophy, or toxic maculopathies like plaquenil maculopathy. Izervay has only been studied in patients with GA secondary to dry AMD and therefore should not be used to treat GA secondary to other conditions.

- Izervay has not been studied in patients with a visual acuity worse than 20/320. Use should be limited to those patients with visual acuity equal to or better than 20/320.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 10/09/202	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/03/2024	Annual review – no changes to the criteria at this time
1.1	Effective Date: 10/12/2023	New policy - this criteria replaces previously approved preliminary criteria
1.0	Effective Date: 08/21/2023	New Policy

Kanuma™ (sebelipase alfa)
HCPCS: J2840

Background Information:

- Lysosomal acid lipase deficiency (LAL-D) is an autosomal recessive lysosomal storage disorder caused by a mutation on the LIPA gene. It is characterized by accumulation of undegraded triglycerides and cholesteryl esters due to a deficiency or insufficient activity of the enzyme lysosomal acid lipase (LAL). Age of onset and phenotypic spectrum are variable and range from an infantile-onset form or Wolman disease with severe clinical course and death before 1 year of age to childhood/adult-onset disease with milder symptoms, historically also known as cholesteryl ester storage disease. The most common symptoms of Wolman's disease include abdominal distension, hepatosplenomegaly, ascites, fibrosis of the liver, vomiting, diarrhea, steatorrhea, malnutrition, failure to thrive, calcification of the adrenal gland, and developmental delays. Patients with cholesteryl ester storage disease present with a range of symptoms depending on the degree of LAL activity including hypercholesterolemia, hypertriglyceridemia, high-density lipoprotein deficiency, abnormal lipid deposits, hepatomegaly, splenomegaly, adrenomegaly, fatty liver disease, and liver fibrosis.

- LAL-D diagnosis is confirmed through identifying reduced lysosomal acid lipase activity in peripheral leukocytes or skin fibroblasts followed by genetic testing that shows the patient has a mutation of the LIPA gene.

- Enzyme replacement is the standard of care in lysosomal acid lipase deficiency. Kanuma is the only enzyme replacement therapy FDA approved for the treatment of pediatric and adult patients with LAL-D. Kanuma has been studied in patients as young as 1 month of age. All patients studied were symptomatic at study entry and showed improvement in liver function, lipid panel, hepatosplenomegaly, and gastrointestinal symptoms.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 10/09/2025	Annual review – no changes made to the criteria at this time
1.4	Effective Date: 10/03/2024	Annual review – no changes made to the criteria at this time
1.3	Effective Date: 10/12/2023	Updated to remove prescriber requirement
1.2	Effective Date: 10/06/2022	Annual review – no changes made to the criteria at this time
1.1	Effective Date: 10/07/2021	Annual review of policy. No changes were made to the criteria.
1.0	Effective Date: 01/01/2021	New Policy

Kebilidi™ (eladocagene exuparvovec-tneq)
HCPCS: J3590

Background Information:

- Aromatic L-amino acid decarboxylase (AADC) deficiency is an autosomal recessive ultrarare disorder caused by a mutation on the DOPA decarboxylase (DDC) gene. It is characterized by a dysfunctional AADC enzyme which is responsible for the production of the neurotransmitters dopamine, serotonin, epinephrine, and norepinephrine. When the enzyme is not functional or has decreased activity, a smaller number of these neurotransmitters are produced leading to neurons not being able to communicate and send signals properly throughout the body.

- The symptoms of AADC deficiency typically begin shortly after birth or when the child is a few months old. There is a wide range of possible symptoms, and the severity of the disease varies among affected individuals. The two most common symptoms are hypotonia in the trunk and oculogyric crises. These crises are characterized by abnormal rotation of the eyeballs and gaze deviation, uncontrolled movements of the head and neck, muscle spasms, agitation, and irritability. They can last several hours and tend to recur every 2 to 5 days. Other movement disorders can be present, such as hypokinesia, hypertonia in the limbs, dystonia, athetosis, chorea, and tremors. Dysfunction of the autonomic nervous system can lead to excessive sweating, hypersalivation, ptosis, nasal congestion, temperature instability, hypotension, and hypoglycemia. Gastrointestinal symptoms including gastric reflux, constipation, or diarrhea are common. Because of the disease itself and because of the numerous possible symptoms, children with AADC deficiency have developmental delays and are not able to reach normal milestones such as walking and talking, have feeding difficulties, and experience failure to thrive. They are prone to many medical complications and might also have difficulty adapting to those complications as their autonomic nervous system is dysfunctional and can react inappropriately to stressors such as surgery or infections.

- The 2017 consensus guidelines for the diagnosis and treatment of AADC deficiency state confirmation of disease involves three core diagnostic tests: a lumbar puncture showing cerebral spinal fluid (CSF) with low levels of 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) and high concentrations of 3-O-methyldopa (3-OMD), L-Dopa, and 5-OH tryptophan (5-HTP); genetic testing showing mutations in the DCC gene; and decreased AADC enzyme activity in the plasma. If genetic diagnosis is performed as the first step, functional confirmation should be completed by measuring AADC enzyme activity in the plasma and/or neurotransmitter metabolites in CSF. Guidelines do recommend performing all three diagnostic tests to confirm diagnosis.

- Management includes a multidisciplinary approach to address the specific needs of the affected individual. Numerous medications can help manage symptoms although the most appropriate treatment regimen greatly varies among affected individuals. There is limited scientific evidence for the efficacy of most treatment options due to the rarity of the disease. First-line treatments include dopamine agonists, monoamine oxidase B [MAO-B] inhibitors, and vitamin B6. Guidelines prefer the use of non-ergot derived dopamine agonists including pramipexole, ropinirole, and rotigotine, and state they should be tried. Guidelines also recommend a trial of MAO-B inhibitors although literature support for use is minimal. Vitamin B6 is considered due to its use as a cofactor for the AADC enzyme and the possibility it may increase residual enzyme

activity. Other medications may also be considered for treatment of patient specific symptoms, such as melatonin, benzodiazepines, or anticholinergics.

- Kebilidi is a disease modifying therapy approved for the treatment of adult and pediatric patients with AADC deficiency. It is an adeno-associated virus (AAV) vector-based gene therapy that replaces the disfunction DDC gene in AADC patients with a functional copy. This indication is approved under accelerated approval based on change from baseline in gross motor milestone achievement at 48 weeks post-treatment. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

- Safety and efficacy of Kebilidi was evaluated in in an open-label, single arm, natural history cohort study of 13 pediatric patients with genetically confirmed, severe AADC deficiency who had achieved skull maturity assessed with neuroimaging. Twelve of the 13 patients had the severe phenotype of AADC deficiency, defined as having no motor milestone achievement at baseline and no clinical response to standard of care therapies. The one remaining patient had a "variant" of the severe disease phenotype with the ability to sit with assistance but with lack of head control. Patients were excluded from the trial if they had any significant structural brain abnormality or had an anti-AAV2 neutralizing antibody titer over 1,200 folds. Patients received a single total dose of 1.8×10^{11} vg of Kebilidi given as four intraputaminal infusions in a single stereotactic neurosurgical procedure. Patients treated with Kebilidi were compared to an external untreated natural history cohort of 43 pediatric patients with severe AADC deficiency who had at least one motor milestone assessment after 2 years of age. The primary surrogate endpoint was gross motor milestone achievement evaluated at week 48 and assessed using the Peabody Developmental Motor Scale, Second Edition (PDMS-2). Gross motor milestone achievement at Week 48 was assessed in 12 of the 13 patients treated in the study with one patient dropping out prior to week 48. Eight (67%) of the 12 treated patients achieved a new gross motor milestone at week 48: 3 patients achieved full head control, 2 patients achieved sitting with or without assistance, 2 patients achieved walking backwards, and the patient with the "variant" severe phenotype was able to sit unassisted. The two patients who achieved walking backwards at week 48 were treated before 2 years of age. The four patients who were unable to achieve new gross motor milestones at week 48 were treated between the ages of 2.8 and 10.8 years. In comparison, none of the 43 untreated patients with the severe phenotype had documented motor milestone achievement at last assessment at a median age of 7.2 years (range 2 to 19 years).

- The plan considers cellular and gene therapies to be proven effective to treat a condition if the following are true: the drug has full Food and Drug Administration approval that was not obtained under the FDA's accelerated approval pathway and the drug met all of its primary endpoint(s) in its pivotal trials, or if confirmatory trials were required, the drug met its primary endpoint(s) in its confirmatory trial(s). Cellular and gene therapies that haven't been proven effective (do not meet the listed criteria) are considered a benefit contract exclusion for most plans.

- Kebilidi was approved under the FDA's accelerated approval pathway, and therefore, is considered experimental/investigational until further confirmatory trials are complete and the medication gets full FDA approval.

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Policy History		
#	Date	Change Description
1.1	Effective Date: 01/20/2026 P&T Date: 12/04/2025	Updated to experimental/investigational designation
1.0	Effective Date: 02/03/2025	New Policy

Keytruda® (pembrolizumab)
HCPCS: J9271

Background Information:

- Keytruda is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the following:

- For the treatment of patients with unresectable or metastatic melanoma

    - For the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB, IIC, or III melanoma following complete resection

- In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations

- In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC

- As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:

- Stage III where patients are not candidates for surgical resection or definitive chemoradiation or

- Metastatic

- As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda

- For the treatment of patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery

- As a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC

- In combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult patients with unresectable advanced or metastatic pleural mesothelioma (MPM)

- In combination with platinum and fluorouracil for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell cancer (HNSCC)

- As a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test

- As a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy

- For the treatment of adult patients with relapsed or refractory classic Hodgkin lymphoma (cHL)

- For the treatment of pediatric patients with refractory cHL or cHL that has relapsed after 2 or more lines of therapy

- For the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL) or who have relapsed after 2 or more prior lines of therapy

- In combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer

- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who

- Are not eligible for any platinum-containing chemotherapy OR

- Have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

- For the treatment of patients with Bacillus Calmette-Guerin (BCG) unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy

- For the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options

    - For the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test

- For the treatment of locally advanced, unresectable, or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, as first-line treatment

    - In combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma

    - For the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

    - In combination with platinum- and fluoropyrimidine-based chemotherapy OR

    - As a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test

- In combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 stage III-IVA cervical cancer

- In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test

- As a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test

- For the treatment of patients with hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen

- In combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC)

- For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)

- In combination with axitinib, for the first-line treatment of patients with advanced renal cell carcinoma (RCC)

- In combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC

- For the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions

    - In combination with carboplatin and paclitaxel, followed by Keytruda as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma

    - In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation

    - As a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation

- For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options

- For the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced sCSS that is not curable by surgery or radiation

- For the treatment of patients with high-risk early-stage triple negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery

- In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA approved test

- The National Comprehensive Cancer Network (NCCN) guidelines category 1 and 2A recommendations are based on uniform NCCN consensus that the recommendations are appropriate. Treatment regimens have been studied and shown to be efficacious when administered as listed in the guidelines. Category 2B and 3 recommendations do not have a high level of evidence to support use and also do not have a uniform consensus from the NCCN panel that the recommendations are appropriate.

- There are no studies to support use of Keytruda following failure. NCCN treatment guidelines also do not recommend use of Keytruda or other PD-L1 checkpoint inhibitors following a previous failure.

- Keytruda has not been studied in patients on chronic immunosuppressant therapy and therefore, should not be used in patients on chronic immunosuppressants.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 05/27/2025 P&T Date: 04/10/2025	Updated to include the trial and failure of preferred products statement

1.5	Effective Date: 02/13/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 02/08/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 02/02/2023	Updated approval length to allow for FDA recommended dosing for at least 60 days and up to 6 months at a time
1.2	Effective Date: 02/10/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 02/04/2021	Updated authorization periods to mirror the recommended treatment duration in the package insert
1.0	Effective Date: 01/01/2021	New Policy

Kisunla™ (donanemab-azbt)
HCPCS: J0175

Background Information:

- Alzheimer's disease is a progressive disease, with pathophysiological changes and clinical manifestations occurring along a continuum. It continues to be a growing health crisis worldwide, affecting patients with the disease and their families. Approximately 7.2 million Americans aged 65 years and older are currently living with Alzheimer's dementia. About 5 million individuals 65 years of age and older may have mild cognitive impairment (MCI) due to Alzheimer's disease, presenting as memory loss and confusion that does not interfere with activities of daily living; however, it may also be secondary to other conditions.

- It is estimated that 10-15% of individuals with MCI go on to develop dementia each year. Within 5 years, approximately 32% of patients with MCI due to Alzheimer's disease progress to dementia. The progression from MCI to dementia marks the point at which the symptoms of Alzheimer's disease will have gradually led to behavior and personality changes, a decline in cognitive abilities that interfere with a person's ability to carry out daily activities independently, and eventually more severe loss of mental function and problems recognizing family and friends. Diagnosis of MCI and of Alzheimer's dementia is based on clinical evaluation determining cognitive and functional status and not solely on test scores, with progressive cognitive decline demonstrated on subsequent follow ups with the patient.

    - Historically, only symptomatic therapies have been available for treating Alzheimer's dementia. These agents do not act on the evolution of the disease. Standard medical treatment for Alzheimer's disease dementia includes cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and N-methyl-D-aspartate (NMDA) antagonists (memantine).

    - All cholinesterase inhibitors are approved for use in mild and moderate Alzheimer's dementia, though donepezil and transdermal rivastigmine are also approved to treat severe Alzheimer's dementia. Memantine, however, is not recommended in mild disease and is only approved for patients with moderate to severe Alzheimer's dementia.

- Current research efforts are focused on identifying and treating patients as early as possible for the best chance of slowing or stopping the progression of Alzheimer's disease. The accumulation of amyloid beta plaques is a defining pathophysiological feature of Alzheimer's disease that can be exhibited as early as the MCI stage of disease and potentially even earlier, before symptoms arise; as such, a great deal of research has focused on clearing amyloid beta from the brain early in the disease process in an attempt to affect disease progression.

- The presence of amyloid beta plaques can be confirmed by an amyloid positron emission tomography (PET) scan or a cerebrospinal fluid (CSF) test via lumbar puncture; these are the longest-standing FDA-cleared methods to confirm amyloid pathology. More recently in May 2025, the FDA cleared the first blood-based biomarker (BBM) test to detect amyloid plaques associated with Alzheimer's disease. Confirmation of the presence of amyloid pathology and other Alzheimer's disease biomarkers has not historically been guideline recommended for the diagnosis of Alzheimer's disease at any point in the disease process, and testing for these biomarkers has primarily been used for research and in settings where the use of FDA-approved therapies requires confirmation of their presence.

- Amyloid PET imaging uses a class of radiopharmaceuticals that detect levels of amyloid in the human brain; examples of such radiopharmaceuticals include Amyvid™ (florbetapir F18), Neuraceq™ (florbetaben F18) and Vizamyl™ (flutemetamol F18). These scans can be interpreted as positive (elevated amyloid) or negative (non-elevated amyloid).If the amyloid PET is positive with abnormal amyloid beta pathology present, cognitive and/or functional testing is necessary to assist in confirming and staging Alzheimer's disease. A positive amyloid PET alone is not diagnostic of Alzheimer's disease.

- CSF testing measures beta-amyloid, specifically beta-amyloid 1-42 which is a marker of amyloid plaques, and total-tau (tTau) and phosphorylated-tau (pTau181) which are markers of neurofibrillary tangles and provide insight into the intensity of neurodegeneration. CSF testing can be useful in differential diagnosis of Alzheimer's disease and other causes of cognitive impairment. In contrast to amyloid PET scans which are typically high cost and limited in availability, the use of CSF assays offers the potential to provide a more affordable and more accessible option to verify amyloid pathology in the brain, as well as detection of both amyloid and tau biomarkers at once.

    - Elevated CSF levels of tTau and pTau181 are associated with faster progression of cognitive decline.

    - There are currently three CSF tests cleared by the FDA for the evaluation of Alzheimer's disease: 1) Lumipulse® G β-Amyloid Ratio (1-42/1-40) test, 2) Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Phospho-Tau (181P) CSF (pTau181) assays (used as a pTau181/Abeta42 ratio), and 3) Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Total-Tau (tTau)CSF assays (used as a tTau/Abeta42 ratio). Refer to Appendix 1 for additional information regarding these tests.

    - As with the amyloid PET, a positive result on CSF test alone is not diagnostic of Alzheimer's disease.

- BBM tests for Alzheimer's disease pathology provide a less invasive, more accessible alternative to amyloid PET and CSF testing. The FDA approved the Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio for the early detection of amyloid plaques associated with Alzheimer's disease in adults aged 55 years and older exhibiting signs and symptoms of the disease. It measures the pTau 217 and β-Amyloid1-42 proteins in human plasma and calculates the numerical ratio of the levels of the two proteins. This ratio correlates to the presence or absence of amyloid plaque, reducing the need for an amyloid PET.

    - The FDA reviewed a clinical study comparing the Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio with amyloid PET scan or CSF test results, 91.7% of individuals with Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio positive results had the presence of amyloid plaques by PET scan or CSF test result, and 97.3 % of individuals with negative results had a negative amyloid PET scan or CSF test result. reviewed by the FDA upon approval.

    - The test is intended for patients presenting in specialized care settings with demonstrable symptoms and signs of cognitive decline and. as with amyloid PET and CSF testing, must be interpreted in conjunction with other clinical information.
    - The FDA found that the Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio is substantially equivalent to the Lumipulse G β-amyloid Ratio (1-42/1-40) CSF test.

    - The Alzheimer's Association's clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings (2025) suggests using a high-sensitivity (≥ 90%) and high-specificity (≥ 90%) BBM test as a confirmatory test in the diagnostic workup of Alzheimer's disease (conditional recommendation, low certainty evidence), allowing BBM testing that meets these thresholds to serves as a substitute for amyloid PET imaging or CSF biomarker testing.

- Updated criteria for the diagnosis and staging of Alzheimer's disease from the Alzheimer's Association Workgroup (2024) and the Alzheimer's Association's clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings (2025) support a biologically based diagnosis of Alzheimer's disease using the above biomarkers, with the caveat that their use in clinical settings is for the evaluation of symptomatic individuals, and not those who are cognitively unimpaired. Additionally, the guidelines acknowledge that though the presence of abnormal biomarkers may be sufficient to confirm Alzheimer's pathology in a symptomatic individual, it should not preclude a clinician from exercising their clinical judgment and searching for other contributors to the patient's symptoms.

- Amyloid pathology can also be found in both cognitively unimpaired adults and in patients with other neurodegenerative disorders; therefore, a positive amyloid PET and/or CSF result alone may be insufficient to establish a diagnosis of Alzheimer's disease or other cognitive disorders. Results from these tests should be interpreted in tandem with other clinical diagnostic evaluations, including cognitive and/or functional testing.

- Validated mental and functional status exams are important tools for assessing cognitive and behavioral functions and measuring activities of daily living and are frequently used when screening older adults for MCI or dementia. They represent a portion of the necessary workup for cognitive impairment or dementia and, like biomarker evaluations, should be interpreted in the context of other clinical information prior to finalizing a diagnosis. Two of the most widely used mental status scales include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), while the Functional Activities Questionnaire (FAQ) is a commonly used functional status exam.

    - The MMSE evaluates temporal and spatial orientation, memory, attention/concentration, language, and visuospatial function. It is scored on a 30-point scale with scores <24 typically regarded as abnormal and indicative of cognitive impairment. Of note, age, education, and race/ethnicity have been shown to affect MMSE scores and should be considered when evaluating an individual patient.

    - The MoCA includes a broader range of cognitive domains, particularly executive abilities, and is able to detect more subtle cognitive deficits that characterize MCI. It evaluates delayed word recall, visuospatial/executive function, language, attention/concentration, and orientation. The MoCA is also scored on a 30-point scale, with scores of 18-25 suggestive of MCI. The cut-off score of 18 is usually considered to separate MCI from Alzheimer's disease, though there is overlap in the scores as AD is determined by the presence of cognitive impairment as well as the loss of functional independence.

    - The FAQ is a subjective 10-item scale that assesses a patient's functional abilities, specifically instrumental activities of daily living (IADL; e.g., preparing meals, performing chores, running errands, traveling outside of one's neighborhood, keeping track of finances). Per-item

scores range from 0-3, with higher scores indicating greater functional impairment. There is no established cut-off score for IADL impairment, though a cut point of 9 (i.e., dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment. The total FAQ score may be useful in differentiating MCI and mild Alzheimer's dementia.

- The Clinical Dementia Rating Scale (CDR) is another validated clinical instrument used to assess and standardize Alzheimer's disease staging that is most often used in research settings and is commonly used to stage dementia progression over time. It is derived from the scores in each of six different categories, or "box scores": memory, orientation, judgment, community affairs, home hobbies, and personal are. Memory is considered the primary category while all others are secondary. According to the CDR Global scores, Alzheimer's disease stages can be defined as unimpaired cognition (CDR Global = 0), MCI due to Alzheimer's (CDR Global = 0.5), mild Alzheimer's dementia (CDR Global = 1), moderate Alzheimer's dementia (CDR Global = 2), and severe Alzheimer's dementia (CDR = 0.3). If the memory box score is 0.5, the CDR Global score can only be 0.5 or 1.

- Ruling out other conditions with similar presentation is essential during diagnostic workup for a patient being evaluated for Alzheimer's disease. Examples of situations where a diagnosis of Alzheimer's disease may be unlikely are listed below; these examples are not all-inclusive. Additionally, when feasible and medically appropriate, patients should be weaned from medications that may contribute to cognitive impairment.

    - Evidence of concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden

    - Features of Lewy Body dementia other than the dementia itself

    - Prominent features of behavioral variant frontotemporal dementia

    - Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia

    - Evidence for another neurological disease or a non-neurological medical comorbidity (e.g., HIV dementia, dementia of Huntington's disease) or medication use that could have a substantial effect on cognition.

    - Vitamin B12 or folate deficiency

    - Psychiatric diagnoses or symptoms, such as hallucinations, anxiety, major depression, or delusions

- The first FDA approved treatment for Alzheimer's disease that could potentially modify the disease process was Aduhelm® (aducanumab-avwa), a human immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta protein, for the treatment of Alzheimer's disease in patients with mild forms of Alzheimer's disease (i.e., MCI due to Alzheimer's or mild Alzheimer's dementia) as this was the population treated in clinical trials and no safety and effectiveness data is available on initiating treatment in earlier or later stages of the disease than were studied. Aduhelm was approved on June 7, 2021, and brought a first-in-class product to market. However, Aduhelm was approved via the accelerated approval pathway based on the reduction in amyloid beta plaques observed in clinical trials; discordant results of Aduhelm's identically designed Phase III EMERGE and ENGAGE trials failed to provide sufficient evidence to support that the lowering of beta amyloid plaque yields a clinical benefit of improved cognition and delayed disease progression. As such, Aduhelm has had minimal impact on the Alzheimer's population in the time since its approval due to uncertain clinical efficacy, negative press surrounding its approval, and questionable long-term safety, and was discontinued in November 2024.

- On January 6, 2023, the FDA granted Biogen/Eisai's Leqembi® (lecanemab-irmb) accelerated approval based on amyloid plaque reduction, making it the second humanized IgG1 monoclonal antibody directed against amyloid beta for the treatment of Alzheimer's disease. On July 6, 2023, the FDA granted full approval to Leqembi for the treatment of AD in patients with MCI or mild dementia stage of disease and confirmed presence of amyloid, the population in which treatment was initiated in clinical trials. The conversion to full approval was supported by data from the Phase III, randomized, placebo-controlled Clarity AD trial that demonstrated the drug's clinical benefit as it relates to amyloid reduction.

    - Clarity AD was conducted over 18 months in patients 50 to 90 years of age with early Alzheimer's disease (i.e., MCI due to Alzheimer's or mild Alzheimer's dementia) and evidence of amyloid on PET or by CSF testing (n=1,795). The primary endpoint was the change from baseline at 18 months in the score on the Clinical Dementia Rating Sum of Boxes (CDR-SB; range, 0-18 with higher scores indicating greater impairment), which assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care). Key secondary endpoints included change in amyloid burden on PET and the scores on a variety of other cognitive and functional assessment scales.

    - Participants treated with Leqembi demonstrated a statistically significant 27% less decline in CDR-SB compared to placebo at 18 months, with a mean difference of -0.45 ($p<0.001$). Other measures of cognition assessed in the trial also showed statistically significant differences favoring the lecanemab treatment arm. It should be noted that statistical significance in the change in CDR-SB may not demonstrate a clinically important change, as some experts suggest that the minimum clinically important difference (MCID) in CDR-SB where a clinically meaningful change to patients, caregivers or clinicians is apparent is generally a change of 1 to 2 points.

    - Change in amyloid burden on PET, another key secondary endpoint, was assessed in a substudy involving 698 participants. At 18 months, the lecanemab group demonstrated a statistically significant larger amount of beta amyloid removal compared with placebo, corresponding to a mean percentage difference of -76.0% ($p<0.001$). 32.4% of those in the lecanemab arm reached amyloid negativity; however, it's worth noting that 7.8% of those in the placebo arm also were amyloid negative at 18 months.

- On July 2, 2024, the FDA approved Eli Lilly's Kisunla for the treatment of Alzheimer's disease, with the caveat that Kisunla should be initiated in patients with MCI or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials. Kisunla marks the third FDA approved anti-amyloid therapy for early symptomatic Alzheimer's disease, and the second to gain full FDA approval based on demonstration

of statistically significant clinical benefit in clinical trials alongside Leqembi. Kisunla targets a specific epitope of beta amyloid found within beta amyloid plaque to facilitate plaque removal. Of the approved anti-amyloid therapies, Kisunla is the first and only agent with evidence to support a limited-duration treatment regimen based on amyloid plaque removal, which could potentially result in fewer infusions and lower treatment costs.

- Approval of Kisunla was based on results from the double-blind, placebo-controlled, parallel-group, Phase III TRAILBLAZER-ALZ-2 trial. Participants (n=1,736) were required to have a diagnosis of MCI or mild dementia stage of Alzheimer's disease with confirmed presence of amyloid pathology based on amyloid PET imaging and a progressive change in memory function for at least 6 months. Eligible participants were also required to have the following during the screening period (i.e. within 63 days) prior to randomization:

    - An MMSE score $\geq$ 20 but $\leq$ 28

    - Baseline brain magnetic resonance imaging (MRI), without findings showing:

        - Increased risk for Amyloid-related imaging abnormalities (ARIA) and/or intracerebral hemorrhage (e.g., findings suggestive of ARIA-E and/or cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm at greatest diameter, more than 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage

        - Presence of other clinically significant lesions that could indicate a dementia diagnosis other than Alzheimer's disease

- Additionally, those included in the study were required to have low/medium or high tau levels based on visual assessment of tau PET imaging, with tau levels considered prognostic of rate of clinical decline. Treatment effect was hypothesized to be more difficult to demonstrate in participants with high tau levels due to their more advanced disease state. Patients ranged from 59 to 86 years old, with a mean age of 73 years. Of the total trial population, 68% had low/medium tau level and 32% had high tau.

- Patients in TRAILBLAZER-ALZ-2 were randomized 1:1 to receive Kisunla (n=860) or placebo (n=876) for a total of up to 72 weeks. Patients who achieved a prespecified reduction in amyloid levels as measured by amyloid PET at weeks 24, 52, and 76 were switched to placebo. Analyses were conducted on two primary populations within the trial: the low/medium tau level population, and the combined population of low/medium plus high tau groups.

    - The primary endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is a combination of the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog13) score, which assesses cognition, and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL) scale score, which assesses function. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance. Other efficacy endpoints evaluated in the trial included the CDR-SB, the ADAS-Cog13, and the ADCS-iADL.

- Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on iADRS compared to placebo at week 76 in both the combined tau group (2.92, $p<0.0001$) and the low/medium tau group (3.25, $p<0.0001$), equating to a 22% slowing of disease progression at week 76 in the combined tau group and 35% slowing of disease progression at week 76 in the low-medium tau group.

- Statistically significant reduction in clinical decline on CDR-SB compared to placebo at week 76 was also demonstrated in the combined tau group (-0.70, $p<0.0001$) and the low/medium tau group (-0.67, $p<0.0001$), correlating to a 29% slowing of disease progression at week 76 in the combined group and a 36% slowing of disease progression in the low/medium tau group. Statistically significant differences between treatment groups were also demonstrated as measured by ADCS-Cog13, and ADCS-iADL at week 76 ($p<0.001$).

- The percentages of patients that reached the prespecified reductions in amyloid and were eligible for switch to placebo based on amyloid PET levels at Week 24, Week 52, and Week 76 timepoints were 17%, 47%, and 69%, respectively. Of note, amyloid PET values could increase after Kisunla treatment is stopped, and there is no data beyond the 76-week trial to guide whether additional Kisunla dosing may be needed for longer-term clinical benefit or how long the amyloid reductions with treatment will last.

- With the approval of Kisunla, we now have two Phase III clinical trials of anti-amyloid therapies (i.e., Clarity AD and TRAILBLAZER-ALZ-2) that have demonstrated an association between amyloid clearance and slowing of cognitive decline in the early Alzheimer's patient population; however, the available evidence, particularly in light of the history of mixed results with previously trialed and failed anti-amyloid therapies in the pipeline, does not unequivocally suggest that amyloid clearance will definitively improve cognitive outcomes. It also remains unclear whether the modest effect on cognition and function demonstrated in the trial will be clinically relevant when used in the real world. There is disagreement among experts about clinical meaningfulness of the magnitude of change in the cognitive outcomes of these trials, and despite the demonstrated statistical significance of the reduction in cognitive decline, we cannot say with certainty that treatment with Kisunla and other anti-amyloid therapies will yield a meaningful change in the patient's status for the benefit to outweigh the risk to treatment. Ultimately, uncertainty remains around the amyloid hypothesis and we do not have adequate data for anti-amyloid therapies to show a correlation between amyloid removal and treatment effect, or differences in outcomes by achieving or not achieving amyloid negativity.

- Any cognitive benefits seen with Kisunla and other anti-amyloid therapies must be weighed against the potential harms of treatment, especially in light of the risk of amyloid-related imaging abnormalities (ARIA) with edema and/or cerebral microhemorrhage. We must also recognize that ARIA risk with real world use may be greater than that in clinical trials due to issues like limited clinical expertise and accessibility issues affecting monitoring. ARIA can occur spontaneously in patients with Alzheimer's disease, with the three main risk factors being exposure to anti-amyloid treatment, presence of pre-treatment microhemorrhages, and APOE ε4 carrier status. Per the labeling, testing for ApoE ε4 status is recommended prior to initiating treatment to inform the risk of ARIA development, though it is not a requirement. The prescriber should educate the patient on test results and its implications, including the risk of ARIA associated with APOE ε4 status. For those opting out of testing, the prescriber should inform patients they can still be treated with Kisunla; however, it cannot be determined if they are at higher risk for ARIA based on APOE ε4 status. The benefits of treatment versus the potential risk of ARIA should be considered prior to initiating treatment with Kisunla. An FDA-authorized test to detect ApoE ε4 alleles to identify those at risk of ARIA is not currently available, and those that are available may vary in accuracy and design.

- Caution should also be exercised when considering administration of Kisunla in patients with factors indicating increased risk of intracerebral hemorrhage, in particular those who need concomitant anticoagulant therapy, as well as when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with Kisunla. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla.

    - Patients with a history of transient ischemic attacks (TIAs) or stroke within the previous 12 months and those with an inadequately controlled bleeding disorder (including platelet count <50,000 or International Normalized Ratio [INR] >1.5) were not eligible to participate in Leqembi clinical trials in early Alzheimer's disease. Given that these factors may increase the risk of intracerebral hemorrhage in this patient population, it is clinically appropriate to apply the same exclusions to Kisunla and other future anti-amyloid therapies.

- The cognitive decline associated with MCI and mild Alzheimer's disease dementia often spans many years. The limited follow up duration of Kisunla's Phase III trial may be insufficient to conclude how effective Kisunla is for treating early Alzheimer's disease in the long term. Ultimately, longer trials are warranted to determine the true efficacy and safety of Kisunla in early Alzheimer's disease. With the lack of information surrounding long-term use, safety, and the real-world effects of Kisunla, a number of questions arise including the appropriate duration of treatment, if or at what point effectiveness will start to decline, and how discontinuation of Kisunla upon reaching undetectable levels of amyloid beta plaque will affect the trajectory of Alzheimer's disease progression.

- Shortly after Kisunla's approval, 36-month results from the open-label, long-term extension study (OLE) of Clarity AD were presented at the 2024 Alzheimer's Association International Conference (AAIC), with data appearing to support that Leqembi continues to work and maintain a similar slowing of cognitive decline as in the original 18-month trial, and that earlier treatment provides greater effect.

- At the 2025 AAIC, four-year results from Leqembi's Clarity AD OLE and 36-month results from Kisunla's TRAILBLAZER-ALZ2 long-term extension (LTE) were presented.

    - In the Clarity AD OLE, the mean change from baseline in CDR-SB in the Leqembi-treated group was -1.75 points after 48 months of treatment compared to a prespecified natural history cohort of Alzheimer's disease. The OLE also demonstrated a 34% reduction in the relative risk of progression to the next disease stage through 4 years of treatment. Additionally, the tau PET substudy of Clarity AD showed that after 4 years of Leqembi treatment, 69% of patients who had low tau levels showed improvement or no decline, and 56% showed improvement from baseline on CDR-SB global cognitive and functional scale.

    - The 4-year OLE data appear to demonstrate consistent benefits of continuous treatment with Leqembi. It should be noted that the 4-year data analysis varied from that conducted at 36 months in that only patients who had been established on Leqembi from inception of the Clarity AD trial were included in the data set.

- Of the 849 patients who had received Leqembi from the beginning of Clarity AD, roughly half had dropped out by the 48-month mark. It is unknown whether these patients experienced disease progression, intolerable side effects, or were lost to follow up due to some other factor. Those who are still enrolled may potentially be doing well because they are more actively managing their disease.

    - Treated patients were again compared to historical data from untreated Alzheimer's patients instead of a matched control group. Differences between the populations could potentially confound outcomes comparisons.

    - The TRAILBLAZER-ALZ 2 LTE included 550 patients who initiated Kisunla in the core study and either continued or were switched to placebo after reaching amyloid negativity. Those receiving placebo in the core study were switched to Kisunla for the LTE to evaluate delayed treatment outcomes (n=657).

    - Compared with an untreated natural history cohort, Kisunla reduced cognitive decline by -0.6 at 18 months and then -1.2 at 36 months on the CDR-SB.

    - Earlier initiation of Kisunla reduced risk of progression to the next disease stage by 27% on the CDR-Global compared to patients with delayed initiation of Kisunla treatment.

    - More than 75% of participants reached amyloid clearance within 76 weeks of starting Kisunla.

    - After up to 2.5 years of observed data in patients who had completed Kisunla treatment, accumulation of amyloid plaque remained slow.

    - The LTE data appears to support that Kisunla continues to provide clinical benefit even after discontinuation of therapy and that earlier treatment provides a more pronounced treatment effect. Caveats to consider when interpreting this data are similar to those of Clarity AD OLE and include that the LTE compared the progression of treated patients to data from a natural history cohort of untreated patients in lieu of a placebo control group, which could potentially confound the results. Additionally, nearly half of patients in the early start Kisunla group dropped out of the study by 36 months for unknown reasons, and, as with Leqembi, those who are still enrolled may potentially be doing well because they are more actively managing their disease.

- Data appears supportive of chronic Leqembi treatment; however, with new data on Kisunla suggesting that patients can stop taking drug once they reach amyloid negativity and treatment benefit continues to grow, the question remains whether there is value, or lack thereof, in continuing treatment of anti-amyloid therapies post-plaque clearance. Controlled head-to-head studies directly comparing the different drugs and treatment regimens are needed to find a resolution to the conflicting conclusions drawn from these extension trials.

- The Centers for Medicare & Medicaid Servies (CMS) recognizes the need for additional information surrounding treatment with Kisunla and other anti-amyloid therapies in the real world. On April 7, 2022, CMS released a national policy for coverage of monoclonal anti-amyloid antibodies approved by the FDA for the treatment of Alzheimer's disease. Under the National Coverage Determination (NCD), Medicare will provide coverage

of FDA approved anti-amyloid antibodies under Coverage with Evidence Development (CED) when furnished in accordance with prespecified coverage criteria laid out in the NCD for patients with a clinical diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia, both with confirmed presence of amyloid beta pathology consistent with Alzheimer's disease.

  - Coverage of these anti-amyloid therapies under CED requires that providers participate in an approved registry to gather information on patient outcomes with treatment to further evaluate whether these products are reasonable and necessary in the Medicare population. The data being collected by these registries is expected to help answer such questions as whether Kisunla and other approved anti-amyloid therapies meaningfully improve health outcomes with real-world use, whether the benefits and harms of these therapies are dependent on select factors in a patient's care, and how the benefits and harms of treatment may change over time. An analysis of this data by CMS for the early Alzheimer's population has not yet been made available to further inform decisions around the long-term use of anti-amyloid therapies.

  - Refer to CMS's NCD: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease for a complete description.

- To date, there is no literature available to support the use of Kisunla in combination with other anti-amyloid therapies.

- On June 10, 2024, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee convened and unanimously voted 11-0 in favor of Kisunla, voting that the available data supported Kisunla's effectiveness in the population enrolled in clinical trials, which excluded patients with low or no tau burden, and that the benefits outweigh the risks of Kisunla in the treatment of Alzheimer's disease in the population enrolled in the clinical trials. Though the vote was unanimous, the committee recognized that questions remained around Lilly's decision to cease dosing once a patient achieved amyloid clearance, particularly with regard to how clinicians in the real world would monitor for and determine when to cease dosing, and they acknowledged that longer-term follow up would be beneficial to provide more clear guidance on both stopping treatment and potentially restarting. The committee also acknowledged that we lack answers to questions surrounding Kisunla's duration of benefit, how to monitor patients between drug stoppage and restarting, and what will happen with side effects in the interim or upon restarting treatment, and that data on patients within different subgroups was lacking, in particular the higher risk ApoE 4 homozygotes and those with little to no representation in the trial which lacked diversity.

- Appropriate use recommendations (AUR) for Kisunla were developed by the Alzheimer's Disease and Related Disorders Therapeutic Workgroup in 2025 to guide implementation of Kisunla use in real-world practice, prioritizing safety considerations and opportunity for effectiveness. The recommendations primarily align with the TRAILBLAZER-ALZ2 inclusion and exclusion criteria with slight variations, often erring more conservatively. AUR include, but are not limited to, the following:

  - Appropriate candidates for Kisunla include patients with MCI or mild dementia due to Alzheimer's disease (Clinical Stage 3 or 4, respectively) with biomarker confirmation of amyloid via PET or CSF testing. CSF biomarker ratios and amyloid PET are considered equivalent in terms of accuracy and performance, and the choice of test may be driven by access concerns or patient preference.

- No BBM tests were FDA approved at the time of AUR publication, and clinical experience and performance in real-world populations were noted as not yet well established. The AUR therefore do not recommend establishing treatment eligibility solely on a positive blood biomarker test; however, in the advent of BBM test approval, the AUR anticipates that these tests will meet appropriate performance criteria to be considered appropriate for establishing eligibility for treatment with Kisunla and other anti-amyloid therapies for Alzheimer's disease.

- APOE genotyping should be performed to inform risk of ARIA development.

- Pre-treatment MRI should be obtained within at most 12 months and ideally less than 6 months of treatment initiation. Those unable to undergo MRI would not be eligible for Kisunla treatment.

- The AUR recommend against using Kisunla in patients receiving anticoagulants, including warfarin, heparin, and direct oral anticoagulants, until additional safety data are available.

- It is reasonable for clinicians to consider discontinuing treatment if amyloid clearance is demonstrated by a negative amyloid PET, typically obtained 12-18 months post-treatment initiation. The rationale for limited treatment duration is based on Kisunla's selectivity for insoluble, mature plaques imaged by PET. Only amyloid PET is validated to assess amyloid plaque clearance in response to treatment; however, the Work Group acknowledges that. knowledge gaps exist around the ability to implement amyloid PET-based stopping rules for Kisunla in clinical practice.

- Based on the current information available, there is insufficient evidence that Kisunla provides a meaningful clinical benefit in patients with mild Alzheimer's disease, and that potential benefits of therapy outweigh the risks of treatment. Therefore, further demonstration of clinical benefit and safety is warranted.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 10/09/2025	Added CSF testing as an option for confirming amyloid-beta pathology to Medicare criteria. Expanded MRI time limits from within the past 60 days to within at most the past 12 months.
1.2	Effective Date: 02/13/2025	Added initial criteria, quantity limits, authorization period, and renewal criteria for Medicare benefit only
1.1	Effective Date: 08/08/2024	New policy. This criteria replaces previously approved preliminary criteria.
1.0	Effective Date: 07/22/2024	New Policy

Krystexxa® (pegloticase)
HCPCS: J2507

Background Information:

- Gout is an inflammatory arthritis that results from hyperuricemia, which contributes to crystallization of monosodium urate monohydrate in the joints. It is one of the most common rheumatic diseases of adulthood with significant morbidity attributed to gout flares (i.e. severe pain, reduced quality of life, decreased physical function).

- One of the mainstays of gout treatment is patient education on diet, lifestyle modifications, and management of comorbidities with a goal of decreasing the risk and frequency of acute gout attacks and lowering serum urate levels. Dietary modifications include limiting consumption of purine-rich meat and seafood, alcohol, and beverages sweetened by high-fructose corn syrup, and encouraging the consumption of vegetables and low-/non-fat dairy products. Elimination of non-essential medications that may induce hyperuricemia should also be considered.

- The American College of Rheumatology (ACR) guidelines for the management of gout (2020) strongly recommend the use of pharmacologic urate-lowering therapy (ULT) in gout patients with any of the following:

    - ≥ 1 subcutaneous tophi

    - Evidence of radiographic damage attributable to gout (i.e., gouty arthropathy)

    - Frequent gout flares defined as ≥ 2 flares annually.

- A target-to-treat strategy is strongly recommended for all patients receiving ULT to optimize patient outcomes by achieving and maintaining a serum urate target of < 6 mg/dL. Dose titration and subsequent dosing should be individualized to the patient and guided by serial serum urate values to achieve the target level as opposed to utilizing a fixed standard-dose strategy for ULT.

- Per the updated guidelines, allopurinol, a xanthine oxidase inhibitor (XOI), is the preferred first-line treatment option for all patients requiring ULT, including those with moderate-to-severe chronic kidney disease (CKD) stage > 3. This recommendation is based on allopurinol's efficacy, safety, tolerability, and low cost. Treatment should be initiated with a lower starting dose (< 100 mg per day) to mitigate safety issues, and gradually titrated to a target serum urate (SU) level of < 6 mg/dL, not to exceed a maximum of 800 mg per day.

- If despite initial treatment with a maximally tolerated or maximally dosed XOI serum urate levels are persistently above target and a patient exhibits continued gout flares (> 2 per year) or has non-resolving subcutaneous tophi, the guidelines conditionally recommend switching to a second XOI (i.e. febuxostat (Uloric®)) over adding a uricosuric agent.

    - The conditional recommendation is due to the fact that no studies directly address the choice of switching to another xanthine oxidase inhibitor or adding a uricosuric agent (e.g., probenecid) when the ULT strategy requires a change.

    - The guidelines strongly recommend initiating febuxostat therapy with a low dose (< 40 mg/day), with subsequent dose titration guided by serum urate levels to a target of < 6 mg/dL, up to a maximum of 80 mg per day.

    - Febuxostat carries a boxed warning of an increased risk of cardiovascular death in gout patients with established cardiovascular disease. Switching to an alternative oral ULT agent is conditionally recommended by the guidelines for patients taking febuxostat with a history of cardiovascular disease (CVD) or a new CVD-related event if available and consistent with other guideline recommendations.

- The 2020 ACR guidelines did not include a formal vote on the indications for uricosuric agents like probenecid; however, they do concur with the 2012 guidelines that add-on therapy with a uricosuric agent to partially responsive XOI treatment can result in improved control of serum urate as demonstrated in several studies of lesinurad added to XOI therapy. Additionally, literature supports the use of probenecid as monotherapy if there is a contraindication or intolerance to XOIs as it provides an alternative mechanism for the treatment of gout. Of note, treatment with uricosuric agents like probenecid should be avoided in patients with a history of nephrolithiasis or moderate-to-severe CKD (stage > 3).

- Patients with gout for whom treatment with XOI, uricosurics, and other interventions have failed to achieve target serum urate levels, and who continue to have frequent gout flares (>2 per year) or who have non-resolving subcutaneous topi are strongly recommended to switch to pegloticase (Krystexxa), an intravenously administered PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. Per the guidelines, Krystexxa is strongly recommended against in the following situations:

    - As first-line therapy, in accordance with FDA approved labeling.

    - For patients with gout who have persistently elevated serum urate levels above target despite maximally tolerated treatments and interventions but have infrequent gout flares (< 2 per year) and no tophi.

- The safety and efficacy of Krystexxa was studied in two replicate randomized, double-blind, placebo-controlled, Phase III trials each conducted over 6 months (i.e. GOUT1 and GOUT2). Krystexxa demonstrated a significantly greater plasma urate lowering response (i.e. sUR < 6mg/dL) than placebo, thereby meeting the primary endpoint of the studies. Patients involved in the trial had a baseline serum uric acid of 8.0mg/dL or

greater, had a contraindication to allopurinol or failed to normalize uric acid levels with the maximum appropriate dose of allopurinol, and had at least one of the following:

  - ≥ 3 gout flares in the previous 18 months
  - ≥ 1 tophus
  - Gouty arthropathy, defined clinically or radiographically as joint damage due to gout.

- Consistent with the FDA approved labeling, Krystexxa should not be used concomitantly with oral urate-lowering therapies and has not been evaluated to treat asymptomatic hyperuricemia or hyperuricemia not associated with gout.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/09/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 06/10/2021	Policy updated to align with 2020 ACR guidelines for management of gout Criteria changes for the following: • Number of flares per year • Serum uric acid requirement • Change t/f of allopurinol to t/f of any XOI • Removal of dose requirement to instead reflect maximally tolerated or maximally titrated dose Probenecid use in combination with any XOI, not just allopurinol
1.0	Effective Date:01/01/2021	New Policy

Kymriah™ (tisagenlecleucel)
HCPCS: Q2042

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

    - Kymriah is indicated for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. It is also approved for use in adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for treatment of patients with primary central nervous system lymphoma.

    - Safety and efficacy was established in two studies. The first was the ELIANA trial, an open-label, multicenter single-arm study of 107 pediatric and young adult patients with relapsed/refractory B-cell precursor ALL. All patients were screened, 88 were enrolled in the study, 68 were treated with CAR-T, and 63 were evaluable for efficacy. Nine percent of the enrolled subjects did not receive the product due to manufacturing failure. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m2 daily for 4 days and cyclophosphamide 500 mg/m2 daily for 2 days) followed by a single dose of Kymriah. Tumors must have had CD19 expressing tumor cells. Patients were included if they were primary refractory defined as not achieving a complete response after 2 cycles of a standard chemotherapy regimen or chemo refractory as defined by not achieving a complete response after 1 cycle of standard chemotherapy for relapsed leukemia; has Philadelphia chromosome positive (Ph+) ALL and were intolerant to or failed 2 lines of tyrosine kinase inhibitor therapy (TKI) or if TKI therapy was contraindicated; they were ineligible for allogeneic stem cell transplant (SCT); or had any bone marrow (BM) relapse after allogenic SCT. Patients were excluded if they had Burkitt's lymphoma, active hepatitis B or C, any uncontrolled infection, grade 2 to 4 graft-versus-host disease, concomitant genetic syndrome with the exception of Down's syndrome, or if they have received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to Kymriah infusion. Efficacy was based on complete remission (CR) within 3 months after infusion, the duration of CR, and proportion

of patients with CR and minimal residual disease (MRD) < 0.01% by flow cytometry (MRD-negative). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52).

- Efficacy was also established in the JULIET trial, an open-label, multicenter, single-arm trial of 160 adult patients with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). Of the160 patients enrolled, 106 patients received Kymriah. Eleven patients enrolled did not receive Kymriah due to manufacturing failure and 38 other patients did not receive Kymriah due to death (n = 16), physician decision (n = 16), or adverse events (n = 3). Patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/µL were excluded from the study. The primary endpoints were complete response (CR) rate and duration of response (DOR). The median time to first response was 0.9 months (range: 0.7 to 3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR as compared to patients with a best response of partial response (PR). Of the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after Kymriah infusion.

- Efficacy and safety were established for follicular lymphoma in the ELARA trial, a phase II, single-arm, multicenter, open-label trial of 94 adult patients with relapsed/refractory follicular lymphoma after at least two prior therapies. Patients were excluded from the study if they had active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, transformed FL, or histological grade 3b FL. To be included, patients had to have measurable disease. The primary endpoint was complete response rate. The CR rate was 69% (95% CI, 60-78). Overall response rate (ORR) was 86% (95% CI, 78-92) with a 12-month progression-free survival (PFS) of 67% (95% CI, 56-76) and nine-month DOR was 76% (95% CI, 65-84). For patients who had a complete response, 12-month PFS was 86% (95% CI, 74-92) and the estimated DOR rate was 87% (95% CI, 75-93).

- Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

- While use of Kymriah has not been established in patients with a creatinine clearance of less than 60 mL/minute, other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National

Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other CAR-T therapies support their use in these patients, Kymriah should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 ml/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.

- The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. While Kymriah has only been studied in patients with a LVEF greater than or equal to 45%, there is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Kymriah should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.

- A provider portal that is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 08/04/2022	Updated to align criteria across all CAR-T policies and include new indication for use in relapsed/refractory FL
1.2	Effective Date: 04/14/2022	Updated to remove CD19 requirement as NCCN guidelines state CAR-T can work without being positive for CD19 disease and add preliminary criteria for use in relapsed/refractory FL
1.1	Effective Date: 08/12/2021	New policy - this policy replaces previously approved criteria that was embedded in Chimeric Antigen Receptor-T Cell Class policy which will be retired
1.0	Effective Date: 01/01/2021	New Policy

Lamzede® (velmanase alfa-tycv)
HCPCS: J0217

Background Information:

- Alpha-mannosidosis is an ultra-rare genetic lysosomal storage disorder that begins in childhood and progresses through adulthood. It is caused by a mutation on the MAN2B1 gene resulting in a deficiency of alpha-mannosidase and the body not being able to breakdown α-mannosyl rich N-linked oligosaccharides. The prevalence is estimated to be 1 in every 500,000 people in the general population.

- The symptoms, progression and severity of alpha-mannosidosis vary widely from one person to another, including between siblings who share the same mutation. Alpha-mannosidosis represents a spectrum or continuum of disease and is highly individualized. The disorder is generally broken down into three separate subtypes: mild (type 1), moderate (type 2), and severe (type 3).

    - The mild form may not be evident until the teen years and progresses slowly. Symptoms typically include muscle weakness and skeletal abnormalities are usually not present. A person with type 1 may have normal cognitive and physical development, however, even this later-onset form may be accompanied by mild to moderate intellectual disability. In some cases, the clinical progression of the disease appears to slow down or stop as the affected individual grows beyond school age.

    - In the moderate form of the disorder, signs of skeletal abnormalities and muscle weakness may appear before ten years of age and progress slowly. Type 2 also may be characterized by distinctive facial features including widely spaced or unevenly developed teeth, macroglossia, prominent forehead, flattened nasal bridge, and prognathism. Abnormalities affecting the eyes may include strabismus, opacity of the cornea, and farsightedness. Ataxia may develop by the age of 20-30.

    - The severe form begins within the first year of life. In most cases, infants appear normal at birth, but the condition grows progressively worse. Type 3 alpha-mannosidosis is characterized by rapid progression of intellectual disability, hydrocephalus, progressive ataxia, hepatosplenomegaly, skeletal abnormalities, and coarse facial features.

- The 2019 diagnostic algorithm for the recognition of alpha-mannosidosis in pediatric and adult patients states analysis of oligosaccharides in urine can be considered as an initial screening procedure. An abnormal result in the measurement of the biomarker is to be considered suggestive of the disease but not sufficient for a definite diagnosis. The determination of enzymatic activity is considered the first choice for screening. Alpha-mannosidosis is confirmed when patients have a biochemical assay showing decreased alpha-mannosidase activity in white blood cells or skin fibroblasts less than 10% of normal and genotyping revealing two pathogenic mutations of the MAN2B1 gene.

- Lamzede is an enzyme replacement therapy for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients. Prior to Lamzede's approval, therapy was supportive and focused on preventing emerging complications, such as, hydrocephalus, otitis media, hearing loss, dental caries, joint symptoms, and kyphoscoliosis. There are studies regarding the use of HSCT in patients with outcomes reported as variable with mixed reports on the neurocognitive impact of the therapy. In 2004, results were published for four patients, aged 3 to 23 years, who had undergone HSCT, suggesting that intellectual function in these patients stabilized with improvement in adaptive skills and verbal memory function. Transplant-related complications are more frequent and severe in older patients, which means HSCT is more of an option in the first years of life making early identification of affected patients critical. Lamzede has not been studied in patients who have undergone a HSCT.

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Policy History		
#	Date	Change Description
1.2	Effective Date: 04/10/2025	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 08/01/2023	New Policy

Lantidra™ (donislecel-jujn)
HCPCS: J3590

Background Information:

- T1D affects nearly 1.9 million people in the United States. It is characterized by the autoimmune-mediated loss of insulin-producing β-cells within the islets of Langerhans in the pancreas and results in a complete deficiency of insulin, which can cause potentially life-threatening conditions like hyper and hypoglycemia, ketoacidosis, and dehydration.

- Of the total population with T1D in the United States, fewer than 80,000 are affected with a rare subset of T1D that is termed "brittle" diabetes. Brittle T1D is particularly difficult to treat as it is characterized by severe instability of blood glucose levels with frequent and unpredictable hypoglycemic episodes that often necessitate hospitalization. These patients have difficulty managing the amount of insulin needed to prevent hyperglycemia without causing frequent episodes of hypoglycemia. Their hypoglycemic episodes are often severe and may contribute to hypoglycemic unawareness, a hallmark of brittle T1D that can make the condition worse as the patient becomes unable to detect drops in blood sugar and may not be able to treat themselves to prevent blood glucose from further dropping. Hypoglycemia unawareness and severe hypoglycemia can lead to injuries resulting from loss of consciousness or seizures and can even be fatal.

- Secondary complications of diabetes like neuropathy, cardiovascular disease, and retinopathy can be common in brittle T1D due to lack of effective glucose control despite intensive insulin therapy, and these patients with difficult-to-treat diabetes exhibit a significant excess mortality.

- The most effective means of preventing or reducing symptoms and chronic complications of T1D is keeping blood glucose levels tightly controlled with insulin therapy. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2025) recommends that most individuals with T1D should be treated with multiple daily injections (MDI) of prandial and basal insulin, or continuous subcutaneous insulin infusion (i.e., an insulin pump). There is no consensus to guide choosing which form of insulin administration is best for a given individual; therefore, the choice of MDI or an insulin pump is based on the needs of the patient. MDI and insulin pump therapy are considered by the ADA to be intensive insulin therapy. Evidence supports intensive insulin therapy as providing the best combination of effectiveness and safety for people with T1D, and the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with MDI or an insulin pump reduced A1C and was associated with improved long-term outcomes.

- Intensive therapy has been associated with higher rates of severe hypoglycemia and hypoglycemia unawareness. The ADA recommends a target A1c goal for most nonpregnant adults of <7% without significant hypoglycemia, and that healthcare professionals consider de-intensifying therapy as appropriate to reduce hypoglycemia risks if this A1c target is too stringent and is limited by hypoglycemia.

- Level 1 hypoglycemia is defined as a measurable glucose concentration < 70 mg/dL but ≥ 54 mg/dL. Level 2 hypoglycemia is defined as blood glucose concentration < 54 mg/dL and is the threshold at which neuroglycopenic symptoms (e.g., warmth, weakness, difficulty thinking/confusion, tiredness/drowsiness) begin to occur and requires immediate action to resolve the event. Patients with level 2 hypoglycemia without adrenergic symptoms (e.g., sweating, hunger, tingling, shakiness, tachycardia, anxiety) or neuroglycopenic symptoms likely have hypoglycemia unawareness. Level 3 hypoglycemia is a severe event characterized by altered mental and/or physical functioning requiring assistance from another person for recover.

- The ADA recommends insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise glycemic targets to avoid hypoglycemia, to partially reverse hypoglycemia unawareness, and reduce risk of future episodes. Recurrent level 2 and/or level 3 hypoglycemia is considered an urgent medical issue that requires intervention with a treatment plan adjustment, behavioral intervention, and possibly the use of technology to assist in identifying and preventing the hypoglycemia.

- In recent years there have been significant advances in diabetes technology to aid in establishing tight glycemic control and minimizing hypoglycemia risk beyond optimizing the traditional self-administration of insulin and self-monitoring of blood glucose. The most commonly utilized diabetes technology includes continuous glucose monitoring (CGM) devices, insulin pumps, and automated insulin delivery (AID) systems. Per the ADA, the type(s) and selection of devices should be individualized based on a person's specific needs, preferences, and skill level.

- Monitoring blood glucose is integral to effective therapy to both monitor for and prevent hypoglycemia and hyperglycemia. Specific needs and goals are individualized to the patient and should guide decisions behind glucose monitoring, including consideration of continuous glucose monitoring (CGM) use. The 2025 Standards of Care recommend that people with diabetes should be offered any type of diabetes device (e.g., insulin pens, glucose meters, CGM or AID systems) and emphasize the need to start CGM early in T1D to promote early achievement of goals. Per the ADA, CGM should be offered for diabetes management in adults on intensive insulin therapy (i.e., MDI or insulin pump) who are capable of using the device safely, and choice of device is individualized to the patient. Sensor-augmented CGM and CGM-assisted pump therapy are available and provide alarm-based prevention of hypoglycemia. Evidence has shown that CGM appears useful in decreasing the time spent in hypoglycemic range in patients with impaired awareness.

- The ADA Standards recommend AID systems be offered for diabetes management to both children and adults with T1D who are capable of using the device safely, and the choice of device is based on the individual's circumstances, preferences, and needs. These devices increase and decrease insulin delivery based on sensor-derived glucose levels to mimic natural insulin delivery. AID systems consist of an insulin pump, a CGM device, and an algorithm for calculating insulin delivery. Basal insulin is adjusted in real time and some systems may also deliver automatic correction doses.

- For children and adults with T1D on MDI who are not able to use or who do not choose an AID system, the ADA recommends offering insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature and/or AID systems. Insulin pumps deliver rapid-acting insulin throughout the day to manage blood glucose levels and have a modest advantage for lowering A1c and reducing severe hyperglycemia rates in children and adults. Sensor-augmented pumps suspend insulin when glucose is low or are predicted to go low within the next half hour and offer an opportunity to reduce hypoglycemia. AID systems are preferred over nonautomated pumps and MDI in patients with T1D.

- The FDA describes AID systems (i.e., a CGM device linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on prespecified glucose thresholds) as "artificial pancreas device systems" (APDS). The components are designed to communicate together to automate maintenance of blood glucose concentrations at a specified range or target to minimize the incidence and severity of hypoglycemic and hyperglycemic events. There are different types of APDS that are approved for use and regulated by the FDA:

- Sensor-augmented pump with low glucose suspend and sensor-augmented pumps with predictive low glucose management (e.g., suspend before low). When the device alarms, the user must take an action to assess their glucose level and resume the insulin infusion.

- A control-to-range system, where insulin dosing is adjusted if glucose levels reach or approach predetermined higher and lower thresholds. Patients still need to monitor their blood glucose, set basal rates for their pump, and give premeal bolus insulin.

- A control-to-target system which sets target glucose levels and tries to maintain them at all times. It is a fully automated system that only requires CGM calibration by the user.

- A hybrid "closed-loop" system, which uses automated insulin delivery with continuous basal insulin delivery adjustments; however, mealtime requires the patient to enter their carbohydrates in order for the pump to determine the required bolus meal dose of insulin. A completely "closed-loop" system is not currently marketed in the United States.

- Beyond intensive insulin therapy and the use of the latest diabetes technologies, treatment for patients with difficult-to-treat brittle T1D is limited to whole pancreas transplant as a means of repairing β-cell function, but it carries both surgical and post-procedural risks and may not be appropriate for all T1D patients. Due to potential adverse effects of lifelong immunosuppression post-transplant, the 2025 ADA guidelines recommend reserving pancreas transplant for those with T1D undergoing simultaneous kidney transplant, following kidney transplant, or those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management.

- An alternative to whole pancreas transplantation is allogenic (donor-derived) islet cell transplantation, which is available in the United States as the FDA approved cell therapy Lantidra (donislecel-jujn). Islet cell transplantation has generally been reserved for patients with frequent and severe metabolic complications who have consistently failed to achieve glycemic control with intensive insulin management. Though it may be

less-invasive than whole pancreas transplant, surgical and post-procedural risks do still exist and risks must be balanced against the potential benefit for each individual patient.

- The FDA approved Lantidra in June 2023 as the first FDA approved allogenic pancreatic islet cell therapy and the first-ever cellular therapy to treat T1D. Lantidra was approved to treat adults with T1D who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. Treatment with Lantidra requires use in conjunction with concomitant immunosuppression. Limitations of use to Lantidra are as follows:

- When considering the risks associated with the infusion procedure and long-term immunosuppression, there is no evidence to show a benefit of administration of Lantidra in patients whose diabetes is well-controlled with insulin therapy or patients with hypoglycemic unawareness who are able to prevent current repeated severe hypoglycemic events (neuroglycopenia requiring active intervention from a third party) using intensive diabetes management (including insulin, devices, and education).

- Repeated intraportal islet infusions are not recommended in patients who have experienced prior portal thrombosis, unless the thrombosis was limited to second- or third-order portal vein branches.

- There is no evidence to support the safe and effective use of Lantidra in patients with liver disease, renal failure, or who have received a renal transplant.

- Approval was based on two prospective, open-label, single-arm studies (Phase I/II UIH-001 and Phase III UIH-002) in which a combined total of 30 adult patients with T1D and hypoglycemic unawareness received at least one infusion and a maximum of three infusions of Lantidra. Patients were required to have a diagnosis of T1D for more than 5 years complicated by reduced awareness of hypoglycemia and/or episodes of severe hypoglycemia that persisted despite intensive insulin management efforts. Severe hypoglycemia was defined as an event with symptoms compatible with hypoglycemia in which the subject required the assistance of another person, and which was associated with either a blood glucose level <50 mg/dL (2.8 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Reduced hypoglycemia awareness was reported by the subject and defined by the absence of adequate autonomic symptoms at glucose values < 54 mg/dL. Subjects with a history of previous transplant were excluded from the trial.

- Of the 30 total participants, 11 received one infusion, 12 received two, and 7 received three. Of the 11 who did not receive a second infusion, 4 were insulin-independent, 3 did not have a donor, and 4 were intolerant to immunosuppression or withdrew from the trial within 6 months. All 7 who received a third infusion were insulin-independent. One subject was unable to geta third infusion due to infection.

- Insulin independence, defined as not requiring exogenous insulin to achieve adequate glycemic control, was one of the efficacy endpoints studied and was achieved by about 70% of subjects. Lantidra demonstrated a mean total duration of insulin independence of 5.1 years in study 1 (n = 10) and 3.2 years in study 2 (n = 20).

- In the pooled population, 5 patients had no days of insulin independence. For the remaining 25 who achieved insulin independence, 4 patients (13.3%) were insulin independent for < 1 year, 12 patients (36.7%) for one to five years, and 9 patients for > 5 years.

- The FDA in their evaluation of Lantidra prior to the April 2021 FDA Cellular, Tissue, and Gene Therapies Advisory Committee meeting considered durable insulin independence without evidence of hypoglycemia a stronger demonstration of clinical benefit compared to adequate glycemic control without serious hypoglycemia. Restoring insulin independence removes the risk of hypoglycemia from exogenous insulin; therefore, for those who have achieved insulin independence, there is a reasonable expectation that severe hypoglycemia would not occur.

- In UIH-001 and UIH-002, changes in severe hypoglycemic event (SHE) occurrence and A1c from baseline at 1 year post last transplant were evaluated as trial endpoints in addition to insulin independence; however, the FDA questioned clinical meaningfulness of the data on these endpoints. Most patients (25/30) did not have a documented SHE in the year prior to their first transplant so an absence in the year after would not represent a change. Additionally, 83% of patients across both trials experienced anemia as a side effect which can falsely lower A1c and affect endpoint interpretation; therefore, there are limitations in being able to demonstrate clinical meaningfulness of A1c improvement from baseline.

- Based on available Lantidra data, the duration of insulin independence cannot be predicted based on the total number of transplants achieved. Additionally, baseline SHE frequency is not predictive of the likelihood of a patient to achieve insulin independence post-Lantidra.

- Lantidra may be administered for up to a maximum of three infusions. To date, there are no data regarding the effectiveness or safety for patients receiving more than three infusions. Per the prescribing information, a second infusion may be performed if the patient does not achieve independence from exogenous insulin within one year of infusion or within one year after losing independence from exogenous insulin after a previous infusion. A third infusion may be performed using the same criteria as for the second infusion.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 12/04/2025	Annual review of criteria performed, no changes were made for Medicare benefit
1.2	Effective Date: 02/13/2025	Annual review of criteria performed, no changes were made
1.1	Effective Date: 02/08/2024	Annual review of criteria performed, no changes were made
1.0	Effective Date: 10/15/2023	New Policy

Leqembi™ (lecanemab-irmb) J0174
Leqembi Iqlik™ (lecanemab-irmb) J3590

Background Information:

- Alzheimer's disease is a progressive disease, with pathophysiological changes and clinical manifestations occurring along a continuum. It continues to be a growing health crisis worldwide, affecting patients with the disease and their families. Approximately 7.2 million Americans aged 65 years and older are currently living with Alzheimer's dementia. About 5 million individuals 65 years of age and older may have mild cognitive impairment (MCI) due to Alzheimer's disease, presenting as memory loss and confusion that does not interfere with activities of daily living; however, it may also be secondary to other conditions.

- It is estimated that 10-15% of individuals with MCI go on to develop dementia each year. Within 5 years, approximately 32% of patients with MCI due to Alzheimer's disease progress to dementia. The progression from MCI to dementia marks the point at which the symptoms of Alzheimer's disease will have gradually led to behavior and personality changes, a decline in cognitive abilities that interfere with a person's ability to carry out daily activities independently, and eventually more severe loss of mental function and problems recognizing family and friends. Diagnosis of MCI and of Alzheimer's dementia is based on clinical evaluation determining cognitive and functional status and not solely on test scores, with progressive cognitive decline demonstrated on subsequent follow ups with the patient.

    - Historically, only symptomatic therapies have been available for treating Alzheimer's dementia. These agents do not act on the evolution of the disease. Standard medical treatment for Alzheimer's disease dementia includes cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and N-methyl-D-aspartate (NMDA) antagonists (memantine).

    - All cholinesterase inhibitors are approved for use in mild and moderate Alzheimer's dementia, though donepezil and transdermal rivastigmine are also approved to treat severe Alzheimer's dementia. Memantine, however, is not recommended in mild disease and is only approved for patients with moderate to severe Alzheimer's dementia.

- Current research efforts are focused on identifying and treating patients as early as possible for the best chance of slowing or stopping the progression of Alzheimer's disease. The accumulation of amyloid beta plaques is a defining pathophysiological feature of Alzheimer's disease that can be exhibited as early as the MCI stage of disease and potentially even earlier, before symptoms arise; as such, a great deal of research has focused on clearing amyloid beta from the brain early in the disease process in an attempt to affect disease progression.

- The presence of amyloid beta plaques can be confirmed by an amyloid positron emission tomography (PET) scan or a cerebrospinal fluid (CSF) test via lumbar puncture; these are the longest-standing FDA-cleared methods to confirm amyloid pathology. More recently in May 2025, the FDA cleared the first blood-based biomarker (BBM) test to detect amyloid plaques associated with Alzheimer's disease. Confirmation of the presence of amyloid pathology and other Alzheimer's disease biomarkers has not historically been guideline recommended for the diagnosis of Alzheimer's

disease at any point in the disease process, and testing for these biomarkers has primarily been used for research and in settings where the use of FDA-approved therapies requires confirmation of their presence.

- Amyloid PET imaging uses a class of radiopharmaceuticals that detect levels of amyloid in the human brain; examples of such radiopharmaceuticals include Amyvid™ (florbetapir F18), Neuraceq™ (florbetaben F18) and Vizamyl™ (flutemetamol F18). These scans can be interpreted as positive (elevated amyloid) or negative (non-elevated amyloid).If the amyloid PET is positive with abnormal amyloid beta pathology present, cognitive and/or functional testing is necessary to assist in confirming and staging Alzheimer's disease. A positive amyloid PET alone is not diagnostic of Alzheimer's disease.

- CSF testing measures beta-amyloid, specifically beta-amyloid 1-42 which is a marker of amyloid plaques, and total-tau (tTau) and phosphorylated-tau (pTau181) which are markers of neurofibrillary tangles and provide insight into the intensity of neurodegeneration. CSF testing can be useful in differential diagnosis of Alzheimer's disease and other causes of cognitive impairment. In contrast to amyloid PET scans which are typically high cost and limited in availability, the use of CSF assays offers the potential to provide a more affordable and more accessible option to verify amyloid pathology in the brain, as well as detection of both amyloid and tau biomarkers at once.

    - Elevated CSF levels of tTau and pTau181 are associated with faster progression of cognitive decline.

    - There are currently three CSF tests cleared by the FDA for the evaluation of Alzheimer's disease: 1) Lumipulse® G β-Amyloid Ratio (1-42/1-40) test, 2) Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Phospho-Tau (181P) CSF (pTau181) assays (used as a pTau181/Abeta42 ratio), and 3) Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Total-Tau (tTau)CSF assays (used as a tTau/Abeta42 ratio). Refer to Appendix 1 for additional information regarding these tests.

    - As with the amyloid PET, a positive result on CSF test alone is not diagnostic of Alzheimer's disease.

- BBM tests for Alzheimer's disease pathology provide a less invasive, more accessible alternative to amyloid PET and CSF testing. The FDA approved the Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio for the early detection of amyloid plaques associated with Alzheimer's disease in adults aged 55 years and older exhibiting signs and symptoms of the disease. It measures the pTau 217 and β-Amyloid1-42 proteins in human plasma and calculates the numerical ratio of the levels of the two proteins. This ratio correlates to the presence or absence of amyloid plaque, reducing the need for an amyloid PET.

    - The FDA reviewed a clinical study comparing the Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio with amyloid PET scan or CSF test results, 91.7% of individuals with Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio positive results had the presence of amyloid plaques by PET scan or CSF test result, and 97.3 % of individuals with negative results had a negative amyloid PET scan or CSF test result.

        - The test is intended for patients presenting in specialized care settings with demonstrable symptoms and signs of cognitive decline, and as with amyloid PET and CSF testing, must be interpreted in conjunction with other clinical information and not as a standalone diagnostic.

        - The FDA found that the Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio is substantially equivalent to the Lumipulse G β-amyloid Ratio (1-42/1-40) CSF test.

    - The Alzheimer's Association's clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings (2025) suggests using a high-sensitivity (≥ 90%) and high-specificity (≥ 90%) BBM test as a confirmatory test in the diagnostic workup of Alzheimer's disease (conditional recommendation, low certainty evidence), allowing BBM testing that meets these thresholds to serve as a substitute for amyloid PET imaging or CSF biomarker testing.

- Updated criteria for the diagnosis and staging of Alzheimer's disease from the Alzheimer's Association Workgroup (2024) and the Alzheimer's Association's clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings (2025) support a biologically based diagnosis of Alzheimer's disease using the above biomarkers, with the caveat that their use in clinical settings is for the evaluation of symptomatic individuals, and not those who are cognitively unimpaired. Additionally, the guidelines acknowledge that though the presence of abnormal biomarkers may be sufficient to confirm Alzheimer's pathology in a symptomatic individual, it should not preclude a clinician from exercising their clinical judgment and searching for other contributors to the patient's symptoms.

- Amyloid pathology can also be found in both cognitively unimpaired adults and in patients with other neurodegenerative disorders; therefore, a positive amyloid PET and/or CSF result alone may be insufficient to establish a diagnosis of Alzheimer's disease or other cognitive disorders. Results from these tests should be interpreted in tandem with other clinical diagnostic evaluations, including cognitive and/or functional testing.

- Validated mental and functional status exams are important tools for assessing cognitive and behavioral functions and measuring activities of daily living and are frequently used when screening older adults for MCI or dementia. They represent a portion of the necessary workup for cognitive impairment or dementia and, like biomarker evaluations, should be interpreted in the context of other clinical information prior to finalizing a diagnosis. Two of the most widely used mental status scales include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), while the Functional Activities Questionnaire (FAQ) is a commonly used functional status exam.

    - The MMSE evaluates temporal and spatial orientation, memory, attention/concentration, language, and visuospatial function. It is scored on a 30-point scale with scores <24 typically regarded as abnormal and indicative of cognitive impairment. Of note, age, education, and race/ethnicity have been shown to affect MMSE scores and should be considered when evaluating an individual patient.

    - The MoCA includes a broader range of cognitive domains, particularly executive abilities, and is able to detect more subtle cognitive deficits that characterize MCI. It evaluates delayed word recall, visuospatial/executive function, language, attention/concentration, and orientation. The MoCA is also scored on a 30-point scale, with scores of 18-25 suggestive of MCI. The cut-off score of 18 is usually

considered to separate MCI from Alzheimer's disease, though there is overlap in the scores as AD is determined by the presence of cognitive impairment as well as the loss of functional independence.

  - The FAQ is a subjective 10-item scale that assesses a patient's functional abilities, specifically instrumental activities of daily living (IADL; e.g., preparing meals, performing chores, running errands, traveling outside of one's neighborhood, keeping track of finances). Per-item scores range from 0-3, with higher scores indicating greater functional impairment. There is no established cut-off score for IADL impairment, though a cut point of 9 (i.e., dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment. The total FAQ score may be useful in differentiating MCI and mild Alzheimer's dementia.

- The Clinical Dementia Rating Scale (CDR) is another validated clinical instrument used to assess and standardize Alzheimer's disease staging that is most often used in research settings and is commonly used to stage dementia progression over time. It is derived from the scores in each of six different categories, or "box scores": memory, orientation, judgment, community affairs, home hobbies, and personal are. Memory is considered the primary category while all others are secondary. According to the CDR Global scores, Alzheimer's disease stages can be defined as unimpaired cognition (CDR Global = 0), MCI due to Alzheimer's (CDR Global = 0.5), mild Alzheimer's dementia (CDR Global = 1), moderate Alzheimer's dementia (CDR Global = 2), and severe Alzheimer's dementia (CDR = 0.3). If the memory box score is 0.5, the CDR Global score can only be 0.5 or 1.

- Ruling out other conditions with similar presentation is essential during diagnostic workup for a patient being evaluated for Alzheimer's disease. Examples of situations where a diagnosis of Alzheimer's disease may be unlikely are listed below; these examples are not all-inclusive. Additionally, when feasible and medically appropriate, patients should be weaned from medications that may contribute to cognitive impairment.

  - Evidence of concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden

  - Features of Lewy Body dementia other than the dementia itself

  - Prominent features of behavioral variant frontotemporal dementia

  - Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia, or

  - Evidence for another neurological disease or a non-neurological medical comorbidity (e.g., HIV dementia, dementia of Huntington's disease) or medication use that could have a substantial effect on cognition.

  - Vitamin B12 or folate deficiency

    - Psychiatric diagnoses or symptoms, such as hallucinations, anxiety, major depression, or delusion

- The first FDA approved treatment for Alzheimer's disease that could potentially modify the disease process was Aduhelm® (aducanumab-avwa), a human immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta protein, for the treatment of Alzheimer's disease in patients with mild forms of Alzheimer's disease (i.e., MCI due to Alzheimer's or mild Alzheimer's dementia) as this was the population treated in clinical trials and no safety and effectiveness data is available on initiating treatment in earlier or later stages of the disease than were studied. Aduhelm was approved on June 7, 2021, and brought a first-in-class product to market. However, Aduhelm was approved via the accelerated approval pathway based on the reduction in amyloid beta plaques observed in clinical trials; discordant results of Aduhelm's identically designed Phase III EMERGE and ENGAGE trials failed to provide sufficient evidence to support that the lowering of beta amyloid plaque yields a clinical benefit of improved cognition and delayed disease progression. As such, Aduhelm has had minimal impact on the Alzheimer's population in the time since its approval due to uncertain clinical efficacy, negative press surrounding its approval, and questionable long-term safety, and was discontinued November 2024.

- On January 6, 2023, the FDA approved Leqembi (lecanemab-irmb) via the accelerated approval pathway as the second humanized IgG1 monoclonal antibody directed against amyloid beta for the treatment of Alzheimer's disease based on amyloid plaque reduction in a Phase II clinical trial, with continued approval contingent upon verification of a clinical benefit in a confirmatory trial. Leqembi is limited to treating patients with MCI due to Alzheimer's or mild Alzheimer's dementia and confirmed presence of amyloid as this was the population evaluated in clinical trials, and no safety or effectiveness data is available on initiating treatment earlier or later in the disease course.

    - Study 201, a Phase II, double-blind, placebo-controlled, dose-finding study of Leqembi in patients with early Alzheimer's disease, served as the basis for FDA's accelerated approval of Leqembi. Study 201 had a 79-week, double-blind, placebo-controlled period, followed by an open-label, extension for up to 206 weeks which was initiated after a gap period of treatment that ranged from 9 to 59 months.

    - The study included patients with MCI due to Alzheimer's disease or mild Alzheimer's dementia and confirmed presence of amyloid pathology (n=856). Participants were randomized to receive one of five doses of Leqembi or matched placebo, with 161 patients randomized to the 10 mg/kg every 2 weeks treatment arm.

    - The Leqembi treatment arms did not meet the primary endpoint of Study 201, which was a change from baseline on a composite score consisting of selected items from various cognitive function tests at week 53. However, those who voluntarily enrolled in the amyloid PET substudy (n=315) and received Leqembi treatment demonstrated significant dose- and time-dependent reduction of amyloid beta plaque from baseline compared to placebo at week 79.

- On July 6, 2023, the FDA granted full approval to Leqembi for the treatment of AD in patients with MCI or mild dementia stage of disease and confirmed presence of amyloid, the population in which treatment was initiated in clinical trials. The conversion to full approval was supported by data from the Phase III Clarity AD trial that demonstrated the drug's clinical benefit as it relates to amyloid reduction.

- Clarity AD was conducted over 18 months in patients 50 to 90 years of age with early Alzheimer's disease (i.e., MCI due to Alzheimer's or mild Alzheimer's dementia) and evidence of amyloid on PET or by cerebrospinal fluid (CSF) testing (n=1,795). Eligible participants were also required to have all of the following during the screening and/or baseline period (i.e., within 60 days) prior to randomization:

    - A global Clinical Dementia Rating (CDR) score of 0.5 (for MCI due to Alzheimer's) or 0.5 – 1.0 (for mild Alzheimer's dementia), and a CDR Memory Box score of 0.5 or greater

    - An MMSE score > 22 but < 30

    - Baseline brain magnetic resonance imaging (MRI), without findings that indicate increased risk for Amyloid-related imaging abnormalities (ARIA) and/or intracerebral hemorrhage (e.g., findings suggestive of ARIA and/or cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm at greatest diameter, more than 4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage

- Participants were excluded from Clarity AD if their history included any of the following:

    - History of transient ischemic attacks (TIA), stroke, or seizures within the previous 12 months

    - Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD

    - Presence of a bleeding disorder that is not under adequate control (including a platelet count <50,000 or International normalized ratio [INR] >1.5)

- Participants were randomly assigned (1:1) to receive Leqembi 10 mg/kg IV every 2 weeks or matched placebo. The primary endpoint was the change from baseline at 18 months in the score on the Clinical Dementia Rating Sum of Boxes (CDR-SB; range, 0-18 with higher scores indicating greater impairment). Key secondary endpoints included change in amyloid burden on PET and the scores on a variety of other cognitive and functional assessment scales.

- Participants treated with Leqembi demonstrated a statistically significant 27% less decline in CDR-SB compared to placebo at 18 months, with a mean difference of -0.45 ($p<0.001$). It should be noted that statistical significance in the change in CDR-SB may not demonstrate a clinically important change, as some experts suggest that the minimum clinically important difference (MCID) in CDR-SB where a clinically meaningful change to patients, caregivers or clinicians is apparent is generally a change of 1 to 2 points.

- The other measures of cognition assessed in the trial also showed statistically significant differences favoring the lecanemab treatment arm; however, the mean differences in these endpoints also did not meet the MCID established by literature or as calculated by the Institute for Clinical and Economic Review (ICER).

    - Changes in amyloid burden on PET, another key secondary endpoint, was assessed in a substudy involving 698 participants. At 18 months, the lecanemab group demonstrated a statistically significant larger amount of beta amyloid removal compared with placebo, corresponding to a mean percentage difference of -76.0% ($p<0.001$). 32.4% of those in the lecanemab arm reached amyloid negativity; however, it's worth noting that 7.8% of those in the placebo arm also were amyloid negative at 18 months.

- Clarity AD was the first clinical trial of an anti-amyloid therapy to demonstrate an association between amyloid clearance and slowing of cognitive decline in the early Alzheimer's patient population; however, the available evidence, particularly in light of the history of mixed results with previously trialed and failed anti-amyloid therapies in the pipeline, does not unequivocally suggest that amyloid clearance will definitively improve cognitive outcomes. It also remains unclear whether the modest effect on cognition and function demonstrated in the trial will be clinically relevant when used in the real world.

- Any cognitive benefits seen with Leqembi and other anti-amyloid therapies must be weighed against the potential harms of treatment, especially in light of the risk of amyloid-related imaging abnormalities (ARIA) with edema and/or cerebral microhemorrhage. Though the incidence of ARIA was numerically lower with Leqembi than with other anti-amyloid therapies in similar clinical trials, the differences in the drugs used and trial design do not allow direct comparisons or support the suggestion that Leqembi may be "safer" than alternative anti-amyloid agents previously studied.

- With the FDA's full approval of Leqembi came the application of a boxed warning regarding ARIA, calling out ApoE ε4 homozygotes in particular who appear to have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. ARIA can occur spontaneously in patients with Alzheimer's disease, with the three main risk factors being exposure to anti-amyloid treatment, presence of pre-treatment microhemorrhages, and APOE ε4 carrier status. Per the labeling, testing for ApoE ε4 status is recommended prior to initiating treatment to inform the risk of ARIA development, though it is not a requirement. The prescriber should educate the patient on test results and its implications, including the risk of ARIA associated with APOE ε4 status. For those opting out of testing, the prescriber should inform patients they can still be treated with Leqembi; however, it cannot be determined if they are at higher risk for ARIA based on APOE ε4 status. The benefits of treatment versus the potential risk of ARIA should be considered prior to initiating treatment with Leqembi. An FDA-authorized test to detect ApoE ε4 alleles to identify those at risk of ARIA is not currently available, and those that are available may vary in accuracy and design.

- Caution should also be exercised when considering Leqembi administration in patients receiving concomitant antithrombotic or thrombolytic medications. Use of these medications (e.g., aspirin, other antiplatelets, anticoagulants) was allowed in Clarity AD if the patient was stable on the dose; however, there was a greater incidence of intracerebral hemorrhage in patients taking Leqembi with antithrombotic (2/79 patients) compared to those receiving placebo (zero patients).

- The cognitive decline associated with MCI and mild Alzheimer's disease dementia often spans many years. The limited follow up duration of Leqembi's Phase II and III trials may be insufficient to conclude how effective Leqembi is for treating early Alzheimer's disease. Ultimately, longer trials are warranted to determine the true efficacy and safety of Leqembi in early Alzheimer's disease. With the lack of information surrounding long-term use, safety, and the real-world effects of Leqembi, a number of questions arise including the appropriate duration of treatment, if or at

what point effectiveness will start to decline, and whether continued treatment with Leqembi is safe and necessary in patients whose amyloid beta plaque has reduced to undetectable levels.

- On April 17, 2023, ICER published its final evidence report of Leqembi for AD. ICER acknowledged that current evidence strongly suggests a Leqembi mildly slows the loss of cognition in patients with early AD; however, the risks of brain swelling and bleeding, particularly when used outside of clinical trials, did not support that average benefits of Leqembi would exceed its risks. Treatment of MCI due to Alzheimer's and mild Alzheimer's dementia with Leqembi was deemed "promising but inconclusive", and after review of the drug's clinical evidence and consideration of Leqembi's other potential benefits, disadvantages, etc., Leqembi at its current price-point represents "low" long-term value for money.

    - The report highlights that uncertainty remains around the amyloid hypothesis and that we do not have adequate data for lecanemab to show a correlation between amyloid removal and treatment effect, or differences in outcomes by achieving or not achieving amyloid negativity.

    - A substantial percentage of patients reached amyloid negativity (by PET scan) in the Phase III trial, but 7.8% of patients in the placebo arm also achieved amyloid negativity. ICER suggests that this finding demonstrates the complexity of Alzheimer's disease pathophysiology and that the role of amyloid in Alzheimer's disease and factors that may impact clinical outcomes are not fully understood.

    - ICER also makes note that the ARIA risk with real world use may be greater than that in clinical trials due to issues like limited clinical expertise and accessibility issues affecting monitoring.

    - Additionally, there are questions of whether the trial results can be generalized to the broader mild Alzheimer's population as the average age of participants in the Phase III trial was just over 71 years of age and included participants with some comorbidities; however, two-thirds of the Alzheimer's population in the US are 75 years of age and older and likely have significant comorbidities.

    - ICER acknowledges that there is disagreement among experts about clinical meaningfulness of the magnitude of change in the cognitive outcomes of these trials and notes that despite the demonstrated statistical significance of the reduction in cognitive decline, we cannot say with certainty that treatment with Leqembi will yield a meaningful change in the patient's status for the benefit to outweigh the risk to treatment.

- Based on the current information available, there is insufficient evidence that Leqembi provides a meaningful clinical benefit in patients with Alzheimer's disease, and that potential benefits of therapy outweigh the risks of treatment. Therefore, demonstration of a clinical benefit is warranted in on-going clinical trials.

- On July 2, 2024, the FDA approved a third anti-amyloid monoclonal antibody, Eli Lilly's Kisunla™ (donanemab-azbt), for the treatment of Alzheimer's disease, with the caveat that Kisunla should be initiated in patients with MCI or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials. Kisunla joins Leqembi as the second drug in this class to gain full FDA approval based on demonstration of statistically significant clinical benefit in clinical trials. Kisunla targets a specific epitope of beta amyloid found within beta

amyloid plaque to facilitate plaque removal. Of the approved anti-amyloid therapies, Kisunla is the first and only agent with evidence to support a limited-duration treatment regimen based on amyloid plaque removal, which could potentially result in fewer infusions and lower treatment costs.

  - Approval of Kisunla was based on safety and efficacy data from the Phase III TRAILBLAZER-ALZ-2 trial, which evaluated a similar population as Clarity AD trial, but with an additional requirement that eligible participants be grouped and analyzed based on tau levels (low/medium or high). Additionally, participants were able to discontinue therapy with Kisunla and switch to placebo if prespecified reductions in amyloid were met during the trial.

  - Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on the integrated Alzheimer's Disease Rating Scale (iADRS) compared to placebo at week 76 in both the combined tau group (2.92, $p<0.0001$) and the low/medium tau group (3.25, $p<0.0001$), equating to a 22% slowing of disease progression at week 76 in the combined tau group and 35% slowing of disease progression at week 76 in the low-medium tau group. Patients on Kisunla also demonstrated a statistically significant reduction in clinical decline on CDR-SB, the secondary endpoint, compared to placebo at week 76. in the combined tau group (-0.70, $p<0.0001$) and the low/medium tau group (-0.67, $p<0.0001$), correlating to a 29% slowing of disease progression at week 76 in the combined group and a 36% slowing of disease progression in the low/medium tau group.

  - The percentages of patients that reached the prespecified reductions in amyloid and were eligible for switch to placebo based on amyloid PET levels at Week 24, Week 52, and Week 76 timepoints were 17%, 47%, and 69%, respectively. Of note, amyloid PET values could increase after Kisunla treatment is stopped, and there is no data beyond the 76-week trial to guide whether additional Kisunla dosing may be needed for longer-term clinical benefit or how long the amyloid reductions with treatment will last.

- Shortly after Kisunla's approval, 36-month results from the open-label, long-term extension study (OLE) of Clarity AD were presented at the 2024 Alzheimer's Association International Conference (AAIC). The mean change from baseline in CDR-SB in the Leqembi-treated group was -0.95 after 36 months of treatment compared to a prespecified natural history cohort of Alzheimer's disease. The OLE also demonstrated a 30% reduction in the relative risk of progressing to the next disease stage. Additionally, the tau PET substudy of Clarity AD showed that with three years of continuous Leqembi treatment, 59% of patients with no or low tau accumulation at baseline showed improvement or no decline, and 51% showed improvement from baseline on the CDR-SB global cognitive and functional scale.

  - The OLE data appears to support that Leqembi continues to work and maintain a similar slowing of cognitive decline as in the original 18-month trial, and that earlier treatment provides greater effect; however, there are potential limitations to consider.

  - Not all patients in the OLE received Leqembi treatment for a full 36-months as at the end of the 18-month Clarity AD trial those on placebo were offered to switch to open-label Leqembi, and historical data based on typical Alzheimer's progression was used to conclude how these patients would respond after 36 months.

    - Additionally, it should be noted that about 600 patients out of 1,800 enrolled dropped out of the 36-month study; it is unclear whether they left due to side effect concerns, issues with follow up, or due to disease progression.

    - The rate of decline can also be questioned. Though the effect seems consistent with a slowing of progression by 0.45 points after 18 months and 0.95 points after 36 months , patients seem to have progressed faster in the latter 18-months of the trial than in the first. In the first 18 months, Leqembi-treated patients progressed by approximately 1.2 points, but at the end of three years they progressed a total of 3.09 points.

- Four-year results from the Clarity AD OLE were presented at the 2025 AAIC. The mean change from baseline in CDR-SB in the Leqembi-treated group was -1.75 points after 48 months of treatment compared to a prespecified natural history cohort of Alzheimer's disease. The OLE also demonstrated a 34% reduction in the relative risk of progression to the next disease stage through 4 years of treatment. Additionally, the tau PET substudy of Clarity AD showed that after 4 years of Leqembi treatment, 69% of patients who had low tau levels showed improvement or no decline, and 56% showed improvement from baseline on CDR-SB global cognitive and functional scale.

    - The 4-year OLE data appear to demonstrate consistent benefits of continuous treatment with Leqembi. It should be noted that the 4-year data analysis varied from that conducted at 36 months in that only patients who had been established on Leqembi from inception of the Clarity AD trial were included in the data set.

    - Of the 849 patients who had received Leqembi from the beginning of Clarity AD, roughly half had dropped out by the 48-month mark. It is unknown whether these patients experienced disease progression, intolerable side effects, or were lost to follow up due to some other factor. Those who are still enrolled may potentially be doing well because they are more actively managing their disease.

    - Treated patients were again compared to historical data from untreated Alzheimer's patients instead of a matched control group. Differences between the populations could potentially confound outcomes comparisons.

- Findings from the TRAILBLAZER-ALZ 2 long-term extension (LTE) study were also at the 2025 AAIC. The LTE included 550 patients who initiated Kisunla in the core study and either continued or were switched to placebo after reaching amyloid negativity. Those receiving placebo in the core study were switched to Kisunla for the LTE to evaluate delayed treatment outcomes (n=657).

    - Compared with an untreated natural history cohort, Kisunla reduced cognitive decline by -0.6 at 18 months and then -1.2 at 36 months on the CDR-SB.

    - Earlier initiation of Kisunla reduced risk of progression to the next disease stage by 27% on the CDR-Global compared to patients with delayed initiation of Kisunla treatment.

    - More than 75% of participants reached amyloid clearance within 76 weeks of starting Kisunla.

    - After up to 2.5 years of observed data in patients who had completed Kisunla treatment, accumulation of amyloid plaque remained slow.

- The LTE data appears to support that Kisunla continues to provide clinical benefit even after discontinuation of therapy and that earlier treatment provides a more pronounced treatment effect. Caveats to consider when interpreting this data are similar to those of Clarity AD OLE and include that the LTE compared the progression of treated patients to data from a natural history cohort of untreated patients in lieu of a placebo control group, which could potentially confound the results. Additionally, nearly half of patients in the early start Kisunla group dropped out of the study by 36 months for unknown reasons, and, as with Leqembi, those who are still enrolled may potentially be doing well because they are more actively managing their disease.

- Data appears supportive of chronic Leqembi treatment; however, with new data on Kisunla suggesting that patients can stop taking drug once they reach amyloid negativity and treatment benefit continues to grow, the question remains whether there is value, or lack thereof, in continuing treatment of anti-amyloid therapies post-plaque clearance. Controlled head-to-head studies directly comparing the different drugs and treatment regimens are needed to find a resolution to the conflicting conclusions drawn from these extension trials.

- The Centers for Medicare & Medicaid Servies (CMS) recognizes the need for additional information surrounding treatment with Leqembi and other anti-amyloid therapies in the real world. **On April 7, 2022, CMS released a national policy for coverage of monoclonal anti-amyloid antibodies approved by the FDA for the treatment of Alzheimer's disease. Under the National Coverage Determination (NCD), Medicare will provide coverage of anti-amyloid antibodies that have been granted full FDA approval under Coverage with Evidence Development (CED) when furnished in accordance with prespecified coverage criteria laid out in the NCD for patients with a clinical diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia, both with confirmed presence of amyloid beta pathology consistent with Alzheimer's disease.**

    - Coverage of anti-amyloid therapies under CED requires that providers participate in an approved registry to gather information on patient outcomes with treatment to further evaluate whether these products are reasonable and necessary in the Medicare population. The data being collected by these registries is expected to help answer such questions as whether Leqembi and other approved anti-amyloid therapies meaningfully improve health outcomes with real-world use, whether the benefits and harms of these therapies are dependent on select factors in a patient's care, and how the benefits and harms of treatment may change over time. An analysis of this data by CMS for the early Alzheimer's population has not yet been made available to further inform decisions around the long-term use of anti-amyloid therapies.

    - Refer to CMS's NCD: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease for a complete description.

- To date, there is no literature available to support the use of Leqembi in combination with other anti-amyloid therapies.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 10/09/2025	Added Leqembi Iqlik and related criteria to the policy Expanded MRI time limits from within the past 60 days to within at most the past 12 months to align with Kisunla
1.4	Effective Date: 02/13/2025	Added initial criteria, quantity limits, authorization period, and renewal criteria for Medicare benefit only
1.3	Effective Date: 08/08/2024	Supporting information updated to include 2024 Alzheimer's Association Workgroup criteria for diagnosis and staging of Alzheimer's and reference to Kisunla.
1.2	Effective Date: 12/14/2023	Supporting information updated to include additional information regarding cognitive testing, Alzheimer's disease diagnosis, and testing for the presence of amyloid. Appendix 1 added to the policy
1.1	Effective Date: 08/10/2023	Updated Medicare criteria to refer to National Coverage Determination vs. National Coverage Analysis
1.0	Effective Date: 04/01/2023	New Policy

Appendix 1: CSF Tests Cleared by the FDA for the Evaluation of Alzheimer's Disease (AD) Biomarkers*

Test	What is measured	Results Interpretation	Notes
Lumipuls β-Amyloid Ratio (1-42/1-40) Fujirebio Diagnostics, Inc.	Ratio of AB 1-42 and AB 1-40 concentrations Determines likelihood of amyloid plaques	Negative (normal): ≥ 0.073 Likely positive (abnormal): 0.059-0.072 Positive (abnormal): ≤ 0.058	AB 1-42 accumulation leads to plaque aggregation and neurotoxicity in AD AB 1-40 remains relatively stable and less prone to aggregating Likely positive and positive results are more likely to be consistent with a positive amyloid PET result; however, these results do not establish a diagnosis of AD or other cognitive disorders.
Elecsys beta-amyloid (1-42) CSF II and Elecsys Phospho-Tau (181P)CSF (pTau181) Roche	Used together to measure the ratio of pTau181 and AB 1-42 concentrations Ratio provides a surrogate marker of amyloid plaque burden with 90% concordance with Amyloid PET imaging	Negative (normal): ratio ≤ lab-designated ratio cut-off Positive (abnormal): ratio > lab-designated ratio cut-off	Increases in CSF pTau181 concentration is associated with more rapid cognitive decline in AD Results below the cut-off reduces the likelihood of AD causing the cognitive impairment Intended to be used in addition to other clinical diagnostic evaluations.
Elecsys beta-amyloid (1-42) CSF II and Elecsys Total-Tau CSF Roche	Used together to measure the ratio of tTau and AB 1-42 concentrations Ratio provides a surrogate marker of amyloid plaque burden concordant with Amyloid PET imaging	Negative (normal): ratio ≤ lab-designated ratio cut-off Positive (abnormal): ratio > lab-designated ratio cut-off	Expected to be available 4th quarter 2023 High CSF tTau can also be found in other neurodegenerative disease (e.g., Creutzfeldt-Jakob disease) Intended to be used in addition to other clinical diagnostic evaluations.

AB – amyloid beta; pTau181 – phosphorylated tau-181; tTau – total Tau

*All are cleared by the FDA for adults 55 and older presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

*Results from different assays may be different and cannot be used interchangeably.

*Results must be interpreted in conjunction with other diagnostic tools, such as neurological examination, neurobehavioral tests, imaging, routine lab tests.

Libtayo® (cemiplimab-rwlc)
HCPCS: J9119

Background Information:

- Libtayo is a programmed death receptor-1 (PD-1) blocking antibody indicated for

- The treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

- The treatment of patients with locally advanced BCC (laBCC) or metastatic BCC (mBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

- As a single agent for first-line treatment of patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is:

- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or

- metastatic

- In combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC with no EGFR, ALK or ROS1 aberrations and is:

- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or

- metastatic

- The efficacy of Libtayo in patients with mCSCC or laCSCC who were not candidates for curative surgery or curative radiation was evaluated in two open-label, multi-center, non-randomized, multicohort studies: study 1423 and study 1540 (EMPOWER-CSCC-1). A total of 108 patients were included in the studies and received Libtayo monotherapy intravenously for up to 48 weeks in study 1423 and 96 weeks in study 1540. Treatment continued until progression of disease, unacceptable toxicity, or completion of planned therapy. Both studies excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; prior treatment with anti–PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or patients with an ECOG score greater than or equal to 2. The study's primary endpoint was objective response rate, or the

percentage of patients who experienced partial shrinkage or complete disappearance of their tumor(s) after treatment. Results showed that 47.2 percent of all patients treated with Libtayo had their tumors shrink or disappear.

- The efficacy of Libtayo in patients with laBCC or mBCC was evaluated in study 1620, an open-label, multi-center, non-randomized study of 112 patients with laBCC or mBCC who had progressed on hedgehog pathway inhibitor (HHI) therapy, had not had an objective response after 9 months on HHI therapy, or were intolerant of prior HHI therapy. Patients received Libtayo monotherapy for up to 93 weeks until disease progression, unacceptable toxicity, or completion of planned treatment. The study excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; prior treatment with anti–PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or patients with an ECOG score greater than or equal to 2. The study's primary endpoints were objective response rate and duration of response. The objective response rate was 27%, including 21% of patients with mBCC and 29% of patients with locally advanced disease. Five patients in the locally advanced subgroup had complete responses with Libtayo. Median duration of response has yet to be reached in the trial, overall or in the metastatic and locally advanced subgroups.

- The efficacy of Libtayo as a single agent in patients with NSCLC was evaluated in study 1624, a randomized, multicenter, open-label, active-controlled trial of 710 patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, or with metastatic NSCLC. Patients received Libtayo monotherapy until RECIST 1.1-defined progressive disease, unacceptable toxicity, or up to 108 weeks. Only patient whose tumors had high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] were eligible for enrollment. The study excluded patients who had undergone prior systemic treatment; patients with EGFR, ALK or ROS1 genomic tumor aberrations; those with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; prior treatment with anti–PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or patients with an ECOG score greater than or equal to 1. The primary endpoints were overall survival and progression free survival. The trial demonstrated a statistically significant improvement in overall survival and progression free survival for patients randomized to Libtayo as compared with chemotherapy.

- The efficacy of LIBTAYO in combination with platinum-based chemotherapy was evaluated in study 16113, a randomized, multi-center, double-blind, active-controlled trial in 466 patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation or with metastatic NSCLC who had not previously received systemic treatment for metastatic NSCLC. Patients were eligible regardless of tumor PD-L1 expression status. Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; or ongoing or recent autoimmune disease that required systemic therapy were ineligible. Subjects were randomized 2:1 to either 350 mg Libtayo plus platinum-based chemotherapy every 3 weeks or placebo plus platinum-based chemotherapy every 3 weeks. The primary endpoint was overall survival. The trial demonstrated a statistically significant improvement in OS for patients randomized to Libtayo in combination with chemotherapy compared with placebo in combination with chemotherapy.

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11. Clinicaltrials.gov. Combinations of cemiplimab (anti-PD-1 antibody) and platinum-based doublet chemotherapy in patients with lung cancer (NCT03409614). Available at: https://clinicaltrials.gov/ct2/show/NCT03409614?term=NCT03409614&draw=2&rank=1. Accessed on November 17, 2022.

Policy History		
#	Date	Change Description
1.6	Effective Date: 06/05/2025 Effective Date: 07/21/2025	Updated criteria to align with standard PD-L1 criteria and updated the authorization period for metastatic non-small cell lung cancer to allow for up to 24 months of therapy
1.5	Effective Date: 02/13/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date:	Annual review of criteria was performed, no changes were made

	02/08/2024	
1.3	Effective Date: 02/02/2023	Updated to include the new FDA approved indication for use in NSCLC in combination with platinum-based chemotherapy and update the approval length to state we will not approve for less than 60 days
1.2	Effective Date: 04/16/2022	Updated approval length to allow for FDA recommended dosing or up to 6 months at a time
1.1	Effective Date: 04/08/2021	Updated to include the new indications of basal cell carcinoma and non-small cell lung cancer
1.0	Effective Date: 01/01/2021	New Policy

Luxturna® (voretigene neparvovec-rzyl)
HCPCS: J3398

Background Information:

- The RPE65 gene is expressed in the retinal pigment epithelium layer and encodes the RPE65 protien. The RPE65 protein is involved in a multi-step process called the visual cycle, which converts light entering the eye into electrical signals that are transmitted to the brain. When light hits photosensitive pigments in the retina, it changes 11-cis retinal, a form of vitamin A, to all-trans retinal. This conversion triggers a series of chemical reactions that create electrical signals that are transmitted to the brain enabling sight. The RPE65 protein then helps convert all-trans retinal back to 11-cis retinal so the visual cycle can begin again. Mutations in the RPE65 gene result in dysfunctional proteins, visual cycle disruption, and visual impairment that progresses to blindness.

- Luxturna is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells defined as retinal thickness greater than 100 microns within the posterior pole and determined by the treating physician. Use in infants under 12 months of age is not recommended because of potential dilution or loss of Luxturna after administration due to the active proliferation of retinal cells occurring in this age group.

- The biallelic mutation of RPE65 is diagnosed with a genetic test. Results of one pathogenic variant in the homozygous state, or the same mutation on both alleles, confirm biallelic RPE65-mediated inherited retinal dystrophy. Compound heterozygousy is when there are two different pathogenic variants. Genetic testing showing compound heterozygousy in the trans configuration, with each allele having one pathogenic variant, confirms biallelic RPE65-mediated inherited retinal dystrophy. Results from genetic tests showing two different pathogenic variants in the cis configuration, where one allele has both variants and the other allele has none, rule out RPE65-mediated inherited retinal dystrophy. If a compound heterozygous state is detected, documentation of a trans configuration will be needed to confirm diagnosis.

- Safety and efficacy were established in an open-label, randomized trial of 31 pediatric and adult patients with biallelic RPE65 mutation-associated retinal dystrophy. Eligible patients had to be at least 3 years of age, have visual acuity less than 20/60 and/or visual field less than 20° in any meridian, and be within the mobility-testing passing range at baseline to allow for measurable improvement. Patients were randomized in a 2:1 ratio to either the intervention group, which received bilateral, sequential subretinal administration of voretigene neparvovec, or the control group. The primary endpoint was change in bilateral mobility testing. Secondary endpoints which were tested statistically in hierarchical order included: a change in full-field light sensitivity threshold testing, change in mobility test score for the first eye injected, and visual acuity testing. Mobility testing and full-field light sensitivity threshold testing were observed one year after the Luxturna injection and found to be significantly improved compared to the control group. The change in visual acuity noted after the first year was not significantly different between the control and Luxturna groups.

References:

1. Luxturna [prescribing information]. Philadelphia, PA: Spark Therapeutics, Inc.; May 2022.
2. Bennett J, Wellman JA, Marshall KA, et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. Lancet. 2016 Aug 13; 388 (10045): 661 - 72.
3. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomized, controlled, open-label, phase 3 trial. Lancet. 2017 Aug 26; 390 (10097): 849 – 60.
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5. Chung DC, Bertelsen M, Lorenz B, et al. The natural history of inherited retinal dystrophy due to biallelic mutations in the RPE65 gene. Am J Ophthalmol. 2019 Mar; 199: 58 – 70.
6. Chung DC, McCague S, Yu ZF, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. Clin Exp Ophthalmol. 2018 Apr; 46 (3): 247 – 59.

Policy History		
#	Date	Change Description
1.5	Effective Date: 04/10/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 04/06/2023	Updated approval length to 3 months
1.2	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made.
1.1	Effective Date: 04/08/2021	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 01/01/2021	New Policy

Lyfgenia™ (lovotibeglogene autotemcel)
HCPCS: J3394

Background Information:

- Lyfgenia is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease (SCD) and a history of vaso-occlusive events (VOEs). Lyfgenia's use is limited in those with α-thalassemia trait (-α3.7/-α3.7) and they may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. Lyfgenia has not been studied in patients with more than two α-globin gene deletions.

- Sickle cell disease is a recessive hemolytic anemia caused by a mutation in the β-globin gene. It is characterized by the formation of sickle hemoglobin (HbS). HbS is less soluble and less elastic than fetal hemoglobin (HbF) or normal adult hemoglobin (HbA). The disease involves multicellular adhesion between sickled red blood cells, white blood cells, platelets, and endothelial cells resulting in vaso-occlusive crises (VOCs). VOCs are the hallmark of SCD and are experienced by approximately 70% of patients. They are recurring, unpredictable, painful events that decrease organ function with complications including stroke, pneumonia, vision loss, pulmonary hypertension, leg ulcers, and sepsis. VOCs are often treated as an emergency requiring acute care and are the number one reason patients with SCD visit the emergency room or are hospitalized.

- Hydroxyurea is a ribonucleotide reductase inhibitor which increases the amount of circulating HbF in the body and has been a mainstay of therapy. It also has been shown to lower the number of circulating leukocytes and reticulocytes altering the expression of adhesion molecules; raise red blood cell (RBC) volume; and improve cellular deformability and rheology, all of which contribute to a decrease in VOCs. The 2014 National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease Guidelines recommend the use of hydroxyurea for the following patient populations:

- In adults with SCD who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period

- In adults with SCD who have sickle cell-associated pain that interferes with daily activities and quality of life

- In adults with SCD who have a history of severe and/or recurrent acute coronary syndrome

- In adults with SCD who have severe symptomatic chronic anemia that interferes with daily activities or quality of life

- In infants 9 months of age and older, children, and adolescents with SCD, offer treatment with hydroxyurea regardless of clinical severity to reduce complications

- In adults and children with SCD who have chronic kidney disease and are taking erythropoietin

- The guidelines recommend starting hydroxyurea at a dose of 15 mg/kg/day for adults and increasing the dose by 5 mg/kg/day every 8 weeks to a maximum dose of 35 mg/kg/day. A clinical response to therapy may take 3 – 6 months. Therefore, a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. Guidelines have not yet been updated to include recommendations for use of gene therapy.

- Safety and efficacy were evaluated in the HGB-206 trial, a single-arm, 24-month, open-label, multicenter Phase I/II study of 32 patients with SCD and a history of at least 4 VOEs in the 24 months prior to study entry. Subjects were excluded from the trial if they had sickle β-thalassemia; were positive for HIV-1 or HIV-2, hepatitis B, or hepatitis C; had inadequate bone marrow function, as defined by an absolute neutrophil count of less than 1000/μL or less than 500/μL for patient taking hydroxyurea or a platelet count less than 120,000/μL without hypersplenism; had advanced liver disease defined as AST, ALT, or total bilirubin greater than 3 times the upper limit of normal; had prior treatment with an allogenic stem cell transplant; or had a prior or current malignancy or immunodeficiency disorder. The primary endpoints were complete resolution of VOEs (VOE-CR) and severe VOEs (sVOE-CR) between 6 months and 18 months after infusion of Lyfgenia. VOEs were defined as any of the following events requiring evaluation at a medical facility: an episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than 2 hours; acute chest syndrome (ACS); acute hepatic sequestration; and/or acute splenic sequestration. Severe VOE (sVOE) were defined as either of the following events: VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit or priapism requiring any level of medical attention. Twenty-eight (88%) of 32 patients achieved VOE-CR between 6 and 18 months after Lyfgenia infusion. Thirty (94%) of 32 patients achieved sVOE-CR during the 6 and 18 months after infusion of Lyfgenia.

- There is currently no data supporting administration of Lyfgenia following administration of another gene therapy. Lyfgenia should not be given following any other gene therapy for SCD as safety and efficacy has not been established.

References:

1. Lyfgenia [prescribing information]. Somerville, MA: Bluebird Bio, Inc.; December 2023.
2. Centers for Disease Control and Prevention. Sickle cell disease: data and statistics. 2023 July 6. Available at: https://www.cdc.gov/ncbddd/sicklecell/data.html. Accessed on: December 11, 2023.
3. Ogedegbe HO. Sickle cell disease: an overview. Laboratory Medicine. 2002; 33(7): 515 – 543.
4. Centers for Disease Control and Prevention. Sickle cell disease: complications and treatments. 2023 July 6. Available at: https://www.cdc.gov/ncbddd/sicklecell/treatments.html. Accessed on December 11, 2023.
5. Brousseau DC, Panepinto JA, Nimmer M, et al. The number of people with sickle-cell disease in the United States: national and state estimates. Am J Hematol. 2010; 85(1): 77 – 78.

6. National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: expert panel report, 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/publications/56-364NFULL.pdf. Accessed on: December 11, 2023.
7. Negre O, Eggimann AV, Beuzard Y, et al. Gene therapy of the β-hemoglobinopathies by lentiviral transfer of the β(A(T87Q))-globulin gene. Hum Gene Ther. 2016; 27 (2): 148–165.
8. Clinicaltrial.gov. A study evaluating the efficacy and safety of lentiGlobin BB305 drug product in beta-thalassemia major and sickle cell disease (NCT02151526). Available at: https://clinicaltrials.gov/ct2/show/NCT02151526?term=lentiglobin&cond=Beta-Thalassemia&draw=1&rank=4. Accessed on December 11, 2023.
9. Clinicaltrials.gov. A study evaluating the safety and efficacy of the lentiGlobin BB305 drug product in severe sickle cell disease (NCT02140554). Available at: https://clinicaltrials.gov/ct2/show/NCT02140554?intr=%22LentiGlobin+BB305%22+OR+%22Zynteglo%22&draw=2&rank=5. Accessed on December 11, 2023.

Policy History		
#	Date	Change Description
1.3	P&T Date: 06/05/2025 Effective Date: 07/21/2025	Updated to include the required use of a provider portal to submit clinical outcomes data after Lyfgenia administration
1.2	Effective Date: 12/12/2024	Updated to allow use of electrophoresis for diagnosis of sickle cell disease and changed the authorization period from 6 months to 12 months
1.1	Effective Date: 02/08/2024	New policy - replaces previously approved preliminary criteria
1.0	Effective Date: 01/02/2024	New Policy

Medical Benefit Oncology Drug Class Policy

Avgemsi™ (gemcitabine) J9184
Alimta (pemetrexed) J9305
Beizray™ (docetaxel) J9174
Bizengri (zenocutuzumab-zbco) J9382
Boruzu® (bortezomib) J9054
Danyelza (naxitamab-gqgk) J9348
Darzalex (daratumumab) J9415
Darzalex FasPro (daratumumab and hyaluronidase-fihj) J9144
Datroway (datopotamab deruxtecan-dlnk) J3590
Docivyx® (docetaxel) J9172
Elahere (mirvetuximab soravtansine-gynx) J9063
Elzonris (tagraxofusp-erzs) J9269
Emrelis (telisotuzumab vedotin-tllv) J3590
Erbitux (cetuximab) J9055
Fyarro (sirolimus protein-bound particles) J9331
Jelmyto (mitomycin) J9281
Kimmtrak (tebentafusp-tebn) J9274
Kyxata™ (carboplatin) C9038
Lymphir (denileukin diftitox-cxdl) J9161
Padcev (enfortumab vedotin-ejfv) J9177
Pemetrexed J9296, J9294, J9297, J9314, J9323, J9322, J9292
Pemfexy (pemetrexed) J9304
Pemrydi RTU (pemetrexed) J9324
Polivy (polatuzumab vedotin-piiq) J9309
Rybrevant (amivantamab-vmjw) J9061
Rybrevant Faspro® (amivantamab and hyaluronidase-lpuj) J3590
Sarclisa (isatuximab-irfc) J9227
Tivdak (tisotumab vedotin-tftv) J9273
Trodelvy (sacituzumab govitecan-hziy) J9317
Vyloy (zolbetuximab-clzb) J1326
Yondelis (trabectedin) J9352
Ziihera (zanidatamab-hrii) J9276

Zusduri (mitomycin) J3590
Zynlonta (loncastuximab tesirine-lpyl) J9359

Background Information:

- Definition of an oncology medication: Any drug (chemotherapy, hormone therapy, gene therapy, biological therapy, or other drug) which is used to treat a cancer (a malignant growth or tumor resulting from the division of abnormal cells) diagnosis. Supportive therapy used for cancer is not in scope of this policy.

- The medications added to the Oncology Drug Class Policy go through a detailed review by a pharmacist to determine if the policy covers the intended criteria for the drug. Each drug is evaluated on the following:

  - Indication
  - Place in therapy
  - Category based on uniform NCCN guidance or category 1 and 2A recommendations
  - Cost of the medication
  - Safety of the medication
  - Genetic testing requirements

References:

1. NCCN guidelines for the specific disease state. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed October 23, 2017.
2. Drug specific package labeling. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed October 23, 2017.

Policy History		
#	Date	Change Description
2.8	Effective Date: 02/12/2026	Updated to include Rybrevant Faspro, Kyxata, Boruzu, and Avgemsi
2.7	Effective Date: 12/04/2025	Updated to include Docivyx and Beizray
2.6	Effective Date: 08/07/2025	Updated to include Emrelis and Zusduri

2.5	Effective Date: 05/27/2025 P&T Date: 04/10/2025	Updated to include the statement that there be no prior failure based on efficacy of a drug with the same mechanism of action unless retrial with the same mechanism of action is guideline recommended or supported by a randomized, controlled clinical trial and added Datroway
2.4	Effective Date: 02/13/2025	Added Ziihera and Bizengri
2.3	Effective Date: 12/12/2024	Added Vyloy
2.2	Effective Date: 10/03/2024	Added Lymphir, Darzalex, and Darzalex FasPro and to remove Adcetris, Besremi, Kyprolis, Romidepsin, and Sylvant
2.1	Effective Date: 04/11/2024	Added Danyelza
2.0	Effective Date: 02/08/2024	Added pemetrexed
1.9	Effective Date: 02/02/2023	Added Elahere and removed Asparlas, Doxil, Evomela, Imlygic, Istodax, Ixempra, Lipodox, Mylotarg, Portrazza, and Zepzelca
1.8	Effective Date: 12/01/2022	Added Pemfexy
1.7	Effective Date: 10/06/2022	Added Kyprolis
1.6	Effective Date: 04/14/2022	Added Kimmtrak, removed Adriamycin, Beleodaq, Dacarbazine, Lartruvo, Oncovin, Pemetrexed, Proleukin, Rubex, Synribo, Torisel, Velcade, and Vyxeos, and updated approval length to allow for FDA recommended dosing or up to 6 months
1.5	Effective Date: 02/10/2022	Added Fyarro
1.4	Effective Date: 12/09/2021	Added Tivdak and Besremi
1.3	Effective Date: 08/12/2021	Added Rybrevant
1.2	Effective Date: 06/10/2021	Added Zynlonta

1.1	Effective Date: 02/04/2021	Added Asparlas and Elzonris
1.0	Effective Date: 01/01/2021	New Policy

Appendix A
Medications covered by this policy include, but not limited to the following:

Drug	HCPCS
Avgemsi™ (gemcitabine)	J9184
Alimta® (pemetrexed)	J9305
Beizray™ (docetaxel)	J9174
Bizengri® (zenocutuzumab-zbco)	J9382
Boruzu® (bortezomib)	J9054
Danyelza® (naxitamab-gqgk)	J9348
Darzalex® (daratumumab)	J9415
Darzalex FasPro® (daratumumab and hyaluronidase-fihj)	J9144
Datroway® (datopotamab deruxtecan-dlnk)	J9011
Docivyx® (docetaxel)	J9172
Elahere® (mirvetuximab soravtansine-gynx)	J9063
Elzonris® (tagraxofusp-erzs)	J9269
Emrelis™ (telisotuzumab vedotin-tllv)	J3590
Erbitux® (cetuximab)	J9055
Fyarro™ (sirolimus protein-bound particles)	J9331
Jelmyto® (mitomycin)	J9281
Kimmtrak® (tebentafusp-tebn)	J9274
Kyxata™ (carboplatin)	C9308
Lymphir™ (denileukin diftitox-cxdl)	J9161
Padcev® (enfortumab vedotin-ejfv)	J9177
Pemetrexed	J9296, J9294, J9297, J9314, J9323, J9322, J9292
Pemfexy™ (pemetrexed)	J9304
Pemrydi RTU® (pemetrexed)	J9324
Polivy® (polatuzumab vedotin-piiq)	J9309
Rybrevant® (amivantamab-vmjw)	J9061
Rybrevant Faspro® (amivantamab and hyaluronidase-lpuj)	J3590
Sarclisa® (isatuximab-irfc)	J9227
Tivdak® (tisotumab vedotin-tftv)	J9273
Trodelvy® (sacituzumab govitecan-hziy)	J9317
Vyloy® (zolbetuximab-clzb)	J1326
Yondelis® (trabectedin)	J9352
Ziihera® (zanidatamab-hrii)	J9276
Zusduri™ (mitomycin)	J3590
Zynlonta® (loncastuximab tesirine-lpyl)	J9359

Niktimvo™ (axatilimab-csfr)
HCPCS: J3590

Background Information:

- Niktimvo is a monoclonal antibody against the colony-stimulating factor 1 (CSF-1) receptor indicated for the treatment of chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg.

- GVHD is a condition that may occur after an aHSCT where the transplanted cells (i.e. graft) from the donor induce an immune response in the recipient (i.e. host), encouraging the host's immune system to attack and reject the newly transplanted cells. GVHD can be categorized as acute (aGVHD) or chronic (cGVHD), with differentiation of the two established by consensus criteria from the National Institutes of Health (NIH). A previous diagnosis of aGVHD is not

required for cGVHD diagnosis. A recent review by Herzog et al reported no prior diagnosis of aGVHD in 39% of patients with cGVHD. Manifestations of cGVHD may span several organ systems or may be restricted to one site. Common characteristics of cGVHD include skin reactions, dry oral mucosa, gastrointestinal (GI) ulcerations, and bronchiolar obstruction. The incidence of cGVHD after aHSCT is about 40%, affecting approximately 140,000 persons in the United States. Analysis from the Chronic GVHD Consortium reported non-relapse mortality rates of 22% after 5 years and 40% (95% confidence interval (CI) 30%–50%) after 12 years. GVHD has been classically divided into acute and chronic variants based on the time of onset using a cutoff of 100 days. However, this conventional division has been challenged by the recognition that signs of acute and chronic GVHD may occur outside of these designated periods. Patients who demonstrate progression of disease by day 5 or nonresponse by day 7 are considered to have corticosteroid resistance

- Acute GVHD manifestations include:
    - Classic maculopapular rash
    - Abdominal cramps with diarrhea
    - Rising serum bilirubin concentration
- Chronic GVHD manifestations include:
    - Skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma
    - Dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract
    - Rising serum bilirubin concentration

- Decrease in lung function

- Joint dysfunction

- Mild disease is treated with local/topical therapy to the affected organ systems. Moderate disease is treated with systemic steroids such as prednisone, with topical therapy added on if needed. For severe disease, prednisone plus an additional immunosuppressive agent is used as initial therapy. Between 40% and 60% of patients with cGVHD do not respond to initial steroid therapy and require escalation to other therapies. Corticosteroids are the primary treatment of cGVHD. Other therapies that may be used include calcineurin inhibitors, an mTOR inhibitor (everolimus or sirolimus), rituximab, mycophenolate mofetil and imatinib. The prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation from 2020 recommend steroids as the first-line treatment for newly diagnosed cGVHD. These guidelines mention that there are no data available allowing the comparison of the efficacy of different second-line treatment options for chronic GVHD, and no indirect comparisons are possible. Therefore, no standard second-line treatment for chronic GVHD exists. The most widely used components of second-line treatment for chronic GVHD, in addition to corticosteroids, are calcineurin inhibitors, extracorporeal photopheresis, ibrutinib (which is approved by the FDA), JAK inhibitors, mycophenolate mofetil, rituximab, mammalian target of rapamycin (mTOR) inhibitors, pentostatin, proteasome inhibitors, and tyrosine kinase inhibitors.

- The National Comprehensive Cancer Network (NCCN) Hematopoietic Cell Transplantation (HCT): Graft-Versus-Host Disease Guidelines version 2.2024 have indicated that Jakafi® is a category 1 recommended agent for steroid-refractory GVHD, both acute and chronic. All other agents are a category 2A including Niktimvo, Rezurock® and Imbruvica®.

- The efficacy of Niktimvo is supported by the AGAVE-201 trial, a Phase II, open-label, randomized, multicenter study that evaluated the efficacy, safety, and tolerability of Niktimvo at three different doses in patients with allogenic hematopoietic stem cell transplant (aHSCT) with recurrent or refractory active cGVHD who had received at least two lines of systemic therapy. Treatment consisted of Niktimvo 0.3 mg/kg administered intravenously every 2 weeks until disease progression, lack of efficacy by 9 months, or unacceptable toxicity. Continued treatment with GVHD prophylaxis and standard care systemic cGVHD therapies (corticosteroids, calcineurin inhibitors, or sirolimus/everolimus) were permitted as long as the patient had been on a stable dose for at least 2 weeks prior to study. Initiation of new systemic cGVHD therapy while on study was not permitted.

- The overall response rate within the first six months of treatment was 75% (95% CI: 64, 84).

- In patients who achieved response, no death or new systemic therapy initiation occurred in 60% (95% CI: 43, 74) of patients for at least 12 months since response.

- The median time to first response was 1.5 months (range, 0.9 to 5.1 months).

- The median duration of response, calculated from first response to progression, death, or new systemic therapies for cGVHD, was 1.9 months (95% CI: 1.6, 3.5).

References:

1. Niktimvo [prescribing information]. Wilmington, DE. Incyte Corporation. August, 2024
2. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology for Hematopoietic Cell Transplantation (HCT): Graft-Versus-Host Disease Guidelines version 2.2024. NCCN.org
3. IPD analytics – New Drug Review – Niktimvo (axatilimab). Payer & Provider Insights. IPDAnalytics.com
4. Incyte Press Release Incyte and Syndax Announce U.S. FDA Approval of Niktimvo™ (axatilimab-csfr) for the Treatment of Chronic Graft-Versus-Host Disease (GVHD) | Incyte/ August 14, 2024.

Policy History		
#	Date	Change Description
1.1	Effective Date: 10/09/2025	Annual Review. No changes were made to the policy/criteria.
1.0	Effective Date: 02/03/2025	New Policy

Nivolumab Products
Opdivo® (nivolumab) J9299
Opdivo Qvantig™ (nivolumab and hyaluronidase-nvhy) J9289

Background Information:

- Opdivo is programmed death receptor-1 (PD-L1)-blocking antibody indicated for the following:
  - Patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab
  - For the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma
  - Adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer in the neoadjuvant setting, in combination with platinum-doublet chemotherapy
  - Adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, as first-line treatment in combination with ipilimumab
  - Adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy
  - Patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo
  - Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab
  - Patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab
  - Patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib

- Patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy

- Adult patients with classical Hodgkin lymphoma that has relapsed or progressed after:

    - Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or

    - 3 or more lines of systemic therapy that includes autologous HSCT

- Patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy

- Adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection of urothelial carcinoma

- Patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy

    - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

    - Adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab

- Patients with hepatocellular carcinoma who have been previously treated with sorafenib in combination with ipilimumab

- Patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy

- Patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.

- Patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with ipilimumab

- Patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy

- Patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy

- Opdivo Qvantig is programmed death receptor-1 (PD-L1)-blocking antibody indicated for the following:

  - Adult patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment following combination treatment with intravenous nivolumab and ipilimumab

  - Adult patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib

  - Adult patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy

  - Adult patients with unresectable or metastatic melanoma

  - Adult patients with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab

  - For the adjuvant treatment of adult patients with completely resected stage IIB, stage IIC, stage III, or stage IV melanoma

  - Adult patients with resectable (tumors ≥ 4 cm or node positive) non-small cell lung cancer in the neoadjuvant setting, in combination with platinum-doublet chemotherapy

  - Adult patients with resectable (tumors ≥ 4 cm or node positive) non-small cell lung cancer and no known EGFR mutations or ALK rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by Opdivo Qvantig monotherapy as adjuvant treatment after surgery

  - Adult patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo Qvantig

- Adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy

- As adjuvant treatment of adult patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection of urothelial carcinoma

- Adult patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine

- Adult patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy

- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

- Adult patients with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab

- Adult patients with hepatocellular carcinoma previously treated with sorafenib and following combination treatment with intravenous nivolumab and ipilimumab

- Adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy

- Adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy

- Adult patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based chemotherapy

- Adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy

- Limitations of Use: Opdivo Qvantig is not indicated in combination with ipilimumab

- The National Comprehensive Cancer Network (NCCN) guidelines category 1 and 2A recommendations are based on uniform NCCN consensus that the recommendations are appropriate. Treatment regimens have been studied and shown to be efficacious when administered as listed in the guidelines. Category 2B and 3 recommendations do not have a high level of evidence to support use and also do not have a uniform consensus from the NCCN panel that the recommendations are appropriate.

- There are no studies to support use of Opdivo or Opdivo Qvantig following failure. NCCN treatment guidelines also do not recommend use of Opdivo or other PD-L1 checkpoint inhibitors following a previous failure.

- Opdivo and Opdivo Qvantig have not been studied in patients on chronic immunosuppressant therapy and therefore, should not be used in patients on chronic immunosuppressants.

- Opdivo and Opdivo Qvantig have not been studied in patients with an ECOG performance status of greater than 2 and therefore, should not be sed in patients with an ECOG score greater than 2.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 05/27/2025 P&T Date: 04/10/2025	Updated to include the trial and failure of preferred products statement and updated the renewal criteria to only allow for only 24 months of therapy for non-small cell lung cancer
1.5	Effective Date: 02/13/2025	Updated to include Opdivo Qvantig
1.4	Effective Date: 04/11/2024	Updated to remove the ECOG requirement
1.3	Effective Date: 04/06/2023	Updated approval length to allow for no less than a 60 day approval duration
1.2	Effective Date: 04/14/2022	Updated approval length to allow for FDA recommended dosing or up to 6 months at a time
1.1	Effective Date: 04/08/2021	Updated to remove the renewal authorization period and only allow for a 6 months approval at a time.
1.0	Effective Date: 01/01/2021	New Policy

Nplate® (romiplostim)
HCPCS: J2802

Background Information:

- Nplate is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy and pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Nplate is also indicated to increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (HS-ARS).

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than ITP. Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. Nplate should not be used in an attempt to normalize platelet counts.

- Idiopathic thrombocytopenic purpura

- ITP, also known as primary immune thrombocytopenic purpura, is an autoimmune, hematologic disorder characterized by persistent thrombocytopenia due to autoantibody binding to platelet antigen(s) causing their premature destruction leading to an increase in bruising and bleeding. Risk of spontaneous bleeding increases as platelet counts drops below 20,000/mm^3. There are estimated to be approximately 60,000 individuals diagnosed with chronic ITP in the U.S.

- For all patients with severe bleeding (eg, intracranial, gastrointestinal) and a platelet count < 30,000/microL, it is recommended that immediate platelet transfusion along with ITP-specific therapy with intravenous immune globulin (IVIG) and high-dose glucocorticoids. Recommendations also suggest ITP-specific therapy for patients with a new diagnosis of ITP and a platelet count < 20,000/microL, even in the absence of bleeding symptoms, because the thrombocytopenia may be persistent and become more severe. Some patients with platelet counts > 30,000/microL may require treatment if they have an increased risk of bleeding (eg, peptic ulcer disease, high risk of falling), other hemostatic defects (eg, use of antiplatelet agents or anticoagulants), a history of bleeding at a higher platelet count, or a need for surgery/invasive procedures.

- Per the American Society of Hematology (ASH) guidelines for immune thrombocytopenia (2019) it is recommended that patients with ITP for ≥ 3 months who are corticosteroid-dependent or unresponsive to corticosteroids and are going to be treated with a TPO-RA, both eltrombopag and romiplostim (Nplate®) are suggested recommendations, with no clinical preference between the two. Doptelet® (avatrombopag) is another TPO-RA approved in 2018 for ITP and is not included in these guidelines. These guidelines make weak recommendations for a TPO-RA over rituximab and for rituximab over splenectomy, but the guideline emphasizes the potential usefulness of all three treatments. Tavalisse® (fostamatinib) is another treatment option that is not included in the ASH guidelines that is often used after a trial of guideline recommended therapies.

- First-line therapy is comprised of oral corticosteroids, immunoglobulins, and splenectomy. These therapies may be undesirable due to the associated complications and/or failure to achieve desirable response. Nplate, administered subcutaneously, is a peptibody that binds to and activates the human thrombopoietin receptor (TPO) leading to increased platelet production.

- Hematopoietic syndrome of acute radiation syndrome

- Acute Radiation Syndrome (ARS) (sometimes known as radiation toxicity or radiation sickness) is an acute illness caused by irradiation of the entire body (or most of the body) by a high dose of penetrating radiation in a very short period of time (usually a matter of minutes).

- The type of radiation exposure event influences the nature of the exposure (i.e., nonionizing versus ionizing radiation), types of ionizing particles (eg, alpha particles, beta particles, neutrons) and/or x-ray/gamma rays, the amount and duration of radiation exposure, and the consequent biologic effects.

- Hematopoietic syndrome (sometimes referred to as bone marrow syndrome) will usually occur with a dose between 0.7 and 10 Gray (Gy: derived unit of ionizing radiation dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per kilogram of matter.)

    - Prodromal symptoms include anorexia, nausea and vomiting. Latent stage includes death of stem cells in bone marrow which can manifest symptoms of anorexia, fever, and malaise with a drop in all blood cell counts causing infection and hemorrhage.

- The recommended dose of Nplate is 10 mcg/kg administered once as a subcutaneous injection, and the dose should be administered as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 Gy. Nplate should be administered regardless of whether a complete blood count can be obtained. The patient's absorbed whole body radiation dose should be estimated based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

- Efficacy studies of Nplate could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Efficacy studies conducted in animals, Nplate's effect on platelet count in healthy human volunteers and its effect on thrombocytopenia in patients with ITP lead to its approval. Nplate significantly increased 60-day survival in irradiated animals. 72.5% survival in the Nplate group compared to 32.5% survival in the control group after total body irradiation of 6.8 Gy.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 04/10/2025	Annual review of criteria was preformed, no changes were made

1.4	Effective Date: 04/11/2024	Annual review of criteria was preformed, no changes were made
1.3	Effective Date: 04/06/2023	Updated the approval duration for HS-ARS to allow for 60 day requirement
1.2	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made.
1.1	Effective Date: 04/08/2021	Updated with new FDA indication for hematopoetic syndrome of acute radiation syndrome (HS-ARS)
1.0	Effective Date: 01/01/2021	New Policy

Nucala® (mepolizumab)
HCPCS: J2182

Background Information:

- Nucala is an interleukin-5 (IL-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.
  - The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).
  - 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.
  - Add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype.
  - Limitations of use: Not for relief of acute bronchospasm or status asthmaticus.

- Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly Churg-Strauss Syndrome)
  - Rare condition affecting 10-15 people per million
  - Mean age of diagnosis is 40 years old, and is rare in children, adolescents, and patients over 65
  - Antineutrophil cytoplasmic antibodies (ANCAs) are found in 40%-60% of patients, but it is unknown whether ANCAs have a pathogenic role or if this is simply a manifestation of EGPA
  - Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia
  - Primarily affects the lungs, followed by the skin, but also involves the cardiovascular, gastrointestinal, renal, and central nervous systems
  - Asthma is the cardinal feature of EGPA, which presents, along with allergic rhinitis and nasal polyps, long before vasculitis and the initial EGPA diagnosis

- The next phase of the disease is typically eosinophilia, high levels of eosinophils in the blood, which are 5% or less in healthy patients and at least 10% up to as high as 60% in EGPA patients

- Vasculitis is the third and final phase of symptoms and includes several organs: fever, fatigue, sudden weight loss, muscle and joint pain, rash, numbness/tingling/loss of strength of hands or feet, chest pain or palpitations, shortness of breath, chronic cough, venous thrombotic events, abdominal pain, blood in stool

- Nucala is the first and only treatment available for adults with EGPA

- Hypereosinophilic syndrome (HES)

    - HES are a group of rare disorders marked by the sustained overproduction of eosinophils with an estimated prevalence between 0.36 to 6.3 per 100,000.

    - In HES, eosinophils damage the tissues that they infiltrate, with common targets that include skin, lung, and GI tract.

    - The goal of therapy is a reduction of the absolute eosinophil count, reduction of signs and symptoms, and prevention of disease progression.

    - Choice of therapy depends on clinical features, specifically whether the patient has clinical features consistent with a myeloid disorder with or without a FIP1L1-PDGFRA positive mutation. Those with myeloid variants are treated initially with imatinib mesylate, while other types of HES are treated with an initial trial of glucocorticoids.

    - Per the guideline for the investigation and management of eosinophilia in the British Journal of Haematology from January 2017, patients with idiopathic HES who do not respond adequately to corticosteroids, or who require prolonged corticosteroid therapy, or who are intolerant of corticosteroids, should be considered for a short trial (4 – 6 weeks) of imatinib, immunomodulatory agents (interferon alpha, ciclosporin or azathioprine), myelosuppressive therapy (hydroxycarbamide) or monoclonal antibody therapy with mepolizumab (anti-interleukin 5), the latter preferably as part of a clinical trial (Grade 2B).

    - Prednisone is the primary initial therapy for symptomatic FIP1L1-PDGFRA-negative HES without indications for emergency treatment. Appropriate starting doses range from 20 mg to 60 mg daily, depending on the severity of the disease manifestations and the degree of eosinophilia at presentation. The dose should be adjusted once the patient responds. Once blood eosinophilia is suppressed and symptoms are controlled, daily glucocorticoid doses are gradually reduced to the lowest dose

that maintains control of the eosinophil count and clinical manifestations. Alternate-day dosing should be the ultimate goal if tolerated.

- Hypereosinophilia of unknown significance (HEus) patients are asymptomatic but have marked eosinophilia (>1,500 cells/microL) and no evidence of clinical manifestations or organ involvement. HEus is not considered a form of HES as eosinophil-mediated complications are absent.

- Those individuals included in Nucala's pivotal trial for HES had eosinophil counts greater than 1,000 cells/microL during screening, a history of 2 or more flares within the past 12 months and had been stable on HES therapy for at least 4 weeks prior to randomization.

- Severe asthma with an eosinophilic phenotype

- Severe asthma requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite therapy. Add-on treatment for severe asthma include LAMA, leukotriene receptor antagonist (LTRA), low dose azithromycin (adults) and biologic agents for severe allergic or severe type 2 asthma. Type 2 inflammation is found in a majority of people with severe asthma and characterized by production of cytokines such as interleukin (IL). Anti-IL5 monoclonal antibodies (Cinqair®, Nucala, and Fasenra™) specifically target the formation of eosinophils and deplete blood eosinophil levels.

- The Global Institute for Asthma (GINA) 2023 Difficult-to-Treat & Severe Asthma Diagnosis and Management guidelines recommend those with sever asthma and Type 2 airway inflammation (blood eosinophils ≥ 150/μL and/or fractional exhaled nitric oxide (FeNO) ≥20 ppb and/or sputum eosinophils ≥2%, and/or asthma is clinically allergen driven) first should consider adherence tests and consider increasing the ICS dose for 3-6 months. Add-on Type 2-targeted biologic therapy should be considered for patients with exacerbations or poor symptom control on high dose ICS-LABA. Local payer eligibility criteria, comorbidities should also be considered. Anti-IL5/anti-IL5R, including Nucala is appropriate in patients with exacerbations in the last year and blood eosinophils ≥ 150/μL.

- A peripheral blood eosinophil count is an indirect way to estimate airway inflammation. A blood eosinophil count ≥ 300 cells/microL may help predict asthmatics who are at increased risk for exacerbations in the next year. Furthermore, a count-response relation exists between blood eosinophil counts and asthma-related outcomes. The European Respiratory Society/American Thoracic Society guidelines from 2020 suggest that treatment of severe asthma be guided by clinical criteria and biomarkers such as blood eosinophil levels or fractional exhaled nitric oxide (FeNO), rather than by clinical criteria alone. In addition, it also suggests that a blood eosinophil count cut-off point of ≥ 150 cells/microliter can be used to guide anti-IL5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations.

- Response to biologic therapy is reviewed after 3-4 months of treatment. If the patient had a good response, the need for each medication should re-evaluated, but do not completely stop inhaled therapy. Consider gradually decreasing or stopping oral steroids first.

- Chronic rhinosinusitis with nasal polyps

    - Chronic rhinosinusitis with nasal polyps (CRSwNP, also referred to as nasal polyposis or nasal polyps) is a chronic inflammatory disease of the nasal passage lining or sinuses that leads to bilateral, benign soft tissue growth referred to as nasal polyps. It affects 5% - 12% of the general population worldwide, often occurring with other immunologic conditions such as allergies and/or asthma. The polyps are characterized by elevated eosinophil levels and are most commonly seen in the third and fourth decade of life.

    - The cornerstone of treatment for nasal polyps is intranasal corticosteroids as well as nasal saline sprays or irrigation. Systemic corticosteroids may also be used short term (10-15 days) to reduce severe polyp inflammation and symptoms like impaired sense of smell or severe nasal blockage.

    - For patients with refractory disease that has not responded to intranasal and oral corticosteroids, biologic therapy and/or functional endoscopic sinus surgery (FESS) may be considered. Surgery must be followed with maintenance therapy with intranasal corticosteroids and other appropriate therapies to prevent recurrence of polyps. No comparative studies or guidelines are available that recommend one treatment option over another for refractory cases.

    - Maintenance therapies are initiated once symptoms have been controlled to minimize inflammation and prevent the regrowth of nasal polyps after surgery. The mainstay of maintenance treatment is intranasal glucocorticoids. Leukotriene inhibitors may also be of benefit as adjunctive therapy, particularly if allergic rhinitis or aspirin-exacerbated respiratory disease are suspected contributing factors.

- COPD with an eosinophilic phenotype

    - The 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report (“GOLD guideline”) defines COPD as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive airflow obstruction. As the definition states, COPD includes chronic bronchitis and/or emphysema, which both make emptying air from the lungs progressively more difficult. Most people with COPD have a combination of both conditions. Dyspnea is the most common symptom of COPD; however, chronic cough and sputum production are also cardinal symptoms. COPD is a common, chronic lung disease. It is estimated that 16 million people in the United States have COPD,

which represents a prevalence of about 6% among adults. COPD is almost exclusively diagnosed in adulthood, typically in adults over the age of 40 years. However, factors/exposures from childhood (e.g. premature birth, respiratory infections, secondhand smoke) are thought to play a role in the future development of COPD in some patients. The prevalence of COPD increases with age, with an estimated prevalence of over 12% in the 65 years of age and older population. COPD is slightly more common in women than men.

- The GOLD guideline's (2025) initial treatment algorithm for COPD is individualized based on an assessment of the patient's symptoms and exacerbation history. These assessments determine the suggested treatment option for patients. Initial pharmacologic treatment includes either a bronchodilator, LABA + LAMA, or LABA + LAMA + ICS depending on a patient's symptoms and exacerbation history. LABA + LAMA + ICS should be considered if blood eosinophils are ≥ 300/μL. Among those with eosinophils ≥ 300/μL and symptoms of chronic bronchitis, consider adding dupilumab (Dupixent®). If a patient's response to initial treatment is appropriate, they should be maintained on that treatment. If a patient does not respond to initial treatment, then adherence, inhaler technique, and possible interfering comorbidities should be checked. Follow-up pharmacologic treatment follows a stepwise approach and is determined based on whether dyspnea or exacerbations are the predominant treatable trait to target. If dyspnea is the predominant trait a patient should start with either a LAMA or LABA and should progress to LABA + LAMA. If exacerbations are the predominant trait, then patients should start with a LABA or LAMA, progress to LABA + LAMA (+ICS if blood eosinophil count ≥ 300 cells/μL) and eventually add on roflumilast (if FEV1 <50% and chronic bronchitis) or add azithromycin (preferred in former smokers). Of note, Nucala has not been included in the GOLD guidelines at this time.

- During Phase III trials, Nucala was evaluated in patients with COPD and an eosinophilic phenotype (blood eosinophil count [BEC] ≥150 cells/μL); Dupixent was evaluated in patients with a BEC ≥300 cells/μL. GSK notes that ~70% of U.S. patients with COPD who continue to experience exacerbations on inhaled triple therapy have a BEC ≥150 cells/μL, representing over one million people.

- There have been no studies supporting co-administration of Nucala with other biologics for approved indications, therefore the safety and efficacy of Nucala in unknown when used in combination with other biologics.

- Clinical reasons a patient may be unable to self-administer Nucala include:

- Patient or caregivers are unable to perform subcutaneous injections with proper technique

- Member requires monthly medical support from the physician

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Table 1: Comparative cumulative daily dosing of inhaled corticosteroids (mcg/day)

Inhaled Corticosteroid	Ages 12 and up			Ages 6-11		
	Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
Beclomethasone dipropionate HFA	100 – 200	>200 – 400	>400	50 – 100	>100 – 200	>200
Budesonide DPI	200 – 400	>400 – 800	>800	100 – 200	>200 – 400	>400
Budesonide nebules	NA	NA	NA	250 – 500	>500 – 1,000	>1,000
Ciclesonide HFA	80 – 160	>160 – 320	>320	80	>80 – 160	>160
Fluticasone furoate DPI	100	NA	200	NA	NA	NA
Fluticasone propionate DPI	100 – 250	>250 – 500	>500	100 – 200	>200 – 400	>400
Fluticasone propionate HFA	100 – 250	>250 – 500	>500	100 – 200	>200 – 500	>500

Mometasone furoate	110 – 220	>220 – 440	>440	110	≥220 - <440	≥440
Triamcinolone acetonide	400 – 1,000	>1,000 – 2,000	>2,000	400 – 800	>800 – 1,200	>1,200

Policy History		
#	Date	Change Description
1.6	Effective Date: 08/07/2025	Added criteria for newly approved COPD with eosinophilic phenotype indication.
1.5	Effective Date: 10/03/2024	Changed the verbiage of "cannot be used in combination with other biologic agents indicated for any of the conditions listed in the policy and other targeted DMARDs" to "Not to be used in combination with other biologics or targeted DMARDs for the same indication" to align with other biologic policies
1.4	Effective Date: 10/12/2023	Annual review of policy; no changes were made to the criteria.
1.3	Effective Date: 10/06/2022	Criteria updated to require self-administration unless clinically unable to do so
1.2	Effective Date: 10/07/2021	Updated to include criteria for new indication: chronic rhinosinusitis with nasal polyps. For asthma indication: Updated LABA and LAMA requirement to LABA or LAMA
1.1	Effective Date: 06/10/2021	Criteria aligned between all biologic asthma agents. Supporting information updated for eosinophilic asthma. The criteria for asthma was previously part of the Biologics for Asthma Policy which will be retired
1.0	Effective Date: 01/01/2021	New Policy

Nulibry® (fosdenopterin)
HCPCS: J1809, C9399

Background Information:

- Nulibry is a cyclic pyranopterin monophosphate (cPMP) substrate replacement therapy indicated for the treatment of molybdenum cofactor deficiency (MoCD) Type A.

- MoCD is an autosomal recessive disorder that results from one of several single gene defects in the biosynthetic pathway of molybdenum cofactor. Molybdenum cofactor deficiency is caused by mutations in the molybdenum cofactor synthesis 1 (MOCS1), MOCS2, or GPHN gene. There are three forms of the disorder, named types A, B, and C (or complementation groups A, B, and C). The forms have the same signs and symptoms but are distinguished by their genetic cause: MOCS1 gene mutations cause type A, MOCS2 gene mutations cause type B, and GPHN gene mutations cause type C.

- Approximately two-thirds of patients have MoCD type A, in which mutations in MOSC1 result in the inability to synthesize the first intermediate in the pathway, cyclic pyranopterin monophosphate (cPMP), and the toxic accumulation of sulfites in blood and urine. Tests reveal that affected individuals have high levels of sulfite, S-sulfocysteine, xanthine, and hypoxanthine in the urine and low levels of uric acid in the blood. A positive sulfite dipstick finding of very fresh urine is highly suggestive of sulfite oxidase deficiency and MoCD; however, a negative dipstick finding should not eliminate suspicion, as urinary sulfite is an unstable compound and prone to false-negative results related to drugs and bacterial degradation.

- MoCD is a rare condition characterized by encephalopathy that worsens over time. Babies with this condition appear normal at birth, but within a week they have difficulty feeding and develop intractable seizures. Brain abnormalities, including atrophy of brain tissue, lead to severe developmental delay; affected individuals usually do not learn to sit unassisted or to speak.

- Biochemical tests, when paired with clinical presentation, can confirm a suspected MoCD diagnosis. A genetic test is the only way to distinguish between MoCD subtypes, and genetic results can take weeks.

- In patients with a presumptive diagnosis of MoCD Type A based on biochemical tests and clinical presentation, confirmation of the diagnosis of MoCD Type A via genetic testing should commence immediately after initiation of Nulibry treatment. Nulibry should be discontinued if the MoCD Type A diagnosis is not confirmed by genetic testing.

- MoCD is estimated to occur in 1 in 100,000 to 200,000 newborns worldwide with a median survival of less than 4 years. More than 100 cases have been reported in the medical literature, although it is thought that the condition is underdiagnosed, so the number of affected individuals may be higher.

- Prior to the development of the synthetic form of cPMP (Nulibry), an E.coli derived recombinant form of cPMP (rcPMP) was in development. Studies for the approval of Nulibry include this rcPMP which has the same active moiety and biologic activity as Nulibry. Studies showed the safety and efficacy of switching patients from rcPMP to cPMP.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 04/10/2025	Annual review of criteria was preformed, no changes were made

1.3	Effective Date: 04/11/2024	Annual review of criteria was preformed, no changes were made
1.2	Effective Date: 04/06/2023	Annual review of criteria was preformed, no changes were made
1.1	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made.
1.0	Effective Date: 11/01/2021	New Policy

Omalizumab Products
Omalizumab-igec J3590
Omlyclo® (omalizumab-igec) J3590
Xolair® (omalizumab) J2357

Background Information:

- Omalizumab is an anti-IgE antibody indicated for: moderate to severe persistent asthma in adults and pediatric 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; chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids as add-on maintenance treatment; IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (type I), including anaphylaxis, that may occur with accidental exposure to one or more foods; and chronic spontaneous urticaria (CSU) in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment. Omalizumab is not indicated for acute bronchospasm or status asthmaticus, the emergency treatment of allergic reactions, including anaphylaxis, or other forms of urticaria.

- Uncontrolled Moderate to Severe Allergic Asthma

- Per the Global Institute for Asthma (GINA) 2024 guidelines, severe asthma is a subset of difficult-to-treat asthma that is uncontrolled despite adherence with maximal optimized high-dose inhaled corticosteroid (ICS)-LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased. Severe asthma requires treatment with high dose ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite therapy. Add-on treatment for severe asthma include LAMA, leukotriene receptor antagonist (LTRA), low dose azithromycin (adults) and biologic agents for severe allergic or severe type 2 asthma. Type 2 inflammation is found in a majority of people with severe asthma and is characterized by production of cytokines such as interleukin and can also include immunoglobulin E (IgE)-mediated events involving mast cells and basophils (in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells). Anti-IgE monoclonal antibodies reduce the levels of circulating IgE and inhibit the binding of IgE to mast cells to prevent activation of the allergic cascade and decrease inflammation.

- The GINA 2024 guidelines stepwise approach recommend those in STEP 5 to add therapy with LAMAs such as tiotropium, to refer for phenotypic assessment for biologic therapy (anti-IgE therapy, anti-IL5 therapy, or anti-IL4 therapy, or anti-thymic stromal lymphopoietin (TSLP) therapy) and to consider high-dose maintenance ICS-formoterol with as-needed low-dose ICS-formoterol as a reliever. Using ICS-formoterol as MART (maintenance and rescue therapy) as recommended by the 2024 GINA guidelines allows for budesonide products to reach high-dose per Table 1. The GINA 2024 guidelines recommend omalizumab as an add-on anti-IgE maintenance therapy option for patients with severe allergic asthma uncontrolled on high-dose ICS-LABA.

- The IgE levels in the coverage criteria are based on the efficacy data from the clinical trials of these medications and where they were found to be most effective.

- Review response to biologic therapy after 4 months of treatment. If the patient had a good response, the need for each medication should re-evaluated, but do not completely stop inhaled therapy. Consider gradually decreasing or stopping oral steroids first.

- Chronic Spontaneous Urticaria

- In the United States approximately 1.5 million people suffer from chronic spontaneous urticaria (CSU; previously referred to as chronic idiopathic urticaria). CSU is characterized by red, swollen, itchy and sometimes painful hives on the skin that spontaneously present and re-occur for more than 6 weeks. Up to 40% of these patients may also experience angioedema.

- Per the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA^2LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF; EuroGuiDerm), and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology guideline for the definition, classification, diagnosis, and management of urticaria (2022) that is endorsed by the American Academy of Dermatology and the American College of Allergy, Asthma and Immunology, CSU is defined as the appearance of wheals, angioedema, or both for more than 6 weeks due to known or unknown causes. Signs and symptoms may occur daily or almost daily or follow an intermittent/recurrent course. CSU may recur after a month or years of a patient achieving full remission.

- The above guidelines recommend a 2^{nd} generation H_1-antihistamine as first-line treatment for all types of urticaria and recommend updosing of a 2^{nd} generation H_1-antihistamine up to fourfold in patients with chronic urticaria unresponsive to a standard-dosed 2^{nd} generation H_1-antihistamine as second-line treatment before other treatments are considered. It is recommended to add omalizumab for the treatment of patients with chronic urticaria unresponsive to high-dose 2^{nd} generation H_1-antihistamines

- Though the guidelines strongly recommend treating according to the aforementioned algorithm, they also recognize that the use of omalizumab may be cost prohibitive. The guidelines therefore acknowledge that other more affordable alternatives with lower levels of evidence may still be relevant in certain contexts based on clinical experience and may be added if the urticaria is unresponsive to 2^{nd} generation H_1-antihistamines alone. The most widely used of these alternatives include doxepin, H_2-antihistamines, immunosuppressives (i.e., methotrexate, mycophenolate mofetil), and leukotriene receptor antagonists (e.g., montelukast).

- 2014 guidelines from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology recommend a similar approach to the 2022 international guidelines; however, the following alternatives are suggested prior to

recommending the addition of omalizumab if the urticaria is unresponsive to 2nd generation H_1-antihistamines alone: adding a different second-generation antihistamine, adding an H_2-antihistamine, adding a leukotriene receptor antagonist, adding a first generation H_1-antihistamine at bedtime, or other adjunctive therapies like hydroxyzine or doxepin.

- Omalizumab and dupilumab are the only other drugs besides H_1-antihistamines that are FDA approved for treatment of CSU. Guidelines have not yet been updated to include dupilumab's place in therapy

- Nasal Polyps

- Chronic rhinosinusitis with nasal polyps (CRSwNP, also referred to as nasal polyposis or nasal polyps) is a chronic inflammatory disease of the nasal passage lining or sinuses that leads to bilateral, benign soft tissue growth referred to as nasal polyps. It affects 5-12% of the general population worldwide, often occurring with other immunologic conditions such as allergies and/or asthma. The polyps are characterized by elevated eosinophil levels and are most commonly seen in the third and fourth decade of life.

- The cornerstone of treatment for nasal polyps is intranasal corticosteroids as well as nasal saline sprays or irrigation. Systemic corticosteroids may also be used short term (10-15 days) to reduce severe polyp inflammation and symptoms like impaired sense of smell or severe nasal blockage.

- For patients with refractory disease that has not responded to intranasal and oral corticosteroids, biologic therapy and/or functional endoscopic sinus surgery (FESS) may be considered. Surgery must be followed with maintenance therapy with intranasal corticosteroids and other appropriate therapies to prevent recurrence of polyps. No comparative studies or guidelines are available that recommend one treatment option over another for refractory cases.

- Maintenance therapies are initiated once symptoms have been controlled to minimize inflammation and prevent the regrowth of nasal polyps after surgery. The mainstay of maintenance treatment is intranasal glucocorticoids. Leukotriene inhibitors may also be of benefit as adjunctive therapy, particularly if allergic rhinitis or aspirin-exacerbated respiratory disease are suspected contributing factors.

- IgE-Mediated Food Allergy

- The 2010 National Institute of Allergy and Infectious Disease Guidelines for the Diagnosis and Management of Food Allergies in the United States recommend suspecting a food allergy in patients presenting with anaphylaxis upon ingestion of food within minutes to hours of ingesting food; in infants, young children, and selected older children diagnosed with certain disorders, such as moderate to severe atopic dermatitis, eosinophilic esophagitis, enterocolitis, enteropathy, and food protein-induced allergic proctocolitis; and in adults diagnosed with eosinophilic esophagitis. Guidelines state the causative food must be identified through one of the following tests: skin prick tests, intradermal tests, total

serum IgE, allergen-specific IgE, atrophy patch test, food elimination diets, or oral food challenges. In clinical trials for Xolair, the diagnosis of food allergy was confirmed through serum specific IgE levels or positive SPT for the following foods: peanuts, milk, eggs, wheat, cashews, hazelnuts, and walnuts. Patients must have had a 4 mm wheal or greater than saline control on SPT or a serum specific IgE greater than or equal to 6 kU_A/L in combination with clinical history of allergic reaction following consumption of peanuts and two other foods to be enrolled in the clinical trial.

- Omalizumab does not provide a cure for food allergies but reduces the risk of potentially life-threatening accidental exposure to food allergens. Omalizumab was superior to placebo in increasing the reaction threshold for peanut, cashew, egg, and milk. Sixty-seven percent of the participants who received omalizumab were able to successfully consume at least 600 mg of peanut protein (cumulative dose, 1044 mg, equivalent to approximately 4 peanuts). This protection still requires ongoing dosing of omalizumab as well as continued avoidance of allergenic foods. Despite the reduced risk of life-threatening reactions, omalizumab does have several serious warnings related to its use, including anaphylaxis. Because of the risk of anaphylaxis, patients should still have a current prescription for epinephrine and access to an epinephrine autoinjector.

- Omalizumab requires patients have total IgE levels of 30 but less than or equal to 1850 IU/mL to adequately dose them based on their body weight. Omalizumab should not be used for IgE-mediated food allergy in those with total IgE levels less than 30 IU/mL or greater than 1850 IU/mL.

- Omalizumab has not been studied and there is no data to support use in combination with other medications used for desensitization of food allergy.

- Omalizumab prefilled syringes for self-administration by certain patients or their caregiver have been approved for all of the indications as the healthcare administered product. Omalizumab prefilled syringes were previously for clinician administration only. Omalizumab's lyophilized powder in single-dose vials can still only be administered by a healthcare provider. Patients should receive 3 doses of omalizumab under the guidance of a healthcare provider due to risk of anaphylaxis before transitioning to self-administration.

- Omalizumab has not been studied and there is no data to support use in combination with other biologic agents and targeted DMARD indicated for any of Omalizumab's approved indications.

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Policy History		
#	Date	Change Description
2.0	Effective Date: 06/05/2025	Updated chronic idiopathic urticaria diagnosis requirement to chronic spontaneous urticaria to align with approved indication
1.9	Effective Date: 04/10/2025	Updated to add Omlyclo and add the statement that coverage will be provided for biosimilar products for FDA labeled indications of the innovator product when criteria are met. The name of the policy was changed from the Xolair Policy to the Omalizumab Products Policy.
1.8	Effective Date: 10/03/2024	Changed the combination use criteria from “Cannot be used in combination with other biologic agents indicated for any of the conditions listed in the policy and other targeted DMARDs” to “Not to be used in combination with other biologics or targeted DMARDs for the same indication” to align with the criteria language in other biologic policies.
1.7	Effective Date: 04/11/2024	Updated to add the new indication of IgE-mediated food allergy
1.6	Effective Date: 10/12/2023	Annual review of policy; no changes were made to the criteria.
1.5	Effective Date: 10/06/2022	Updated criteria to require those who are clinically able to do so, to self-administer Xolair prefilled syringe after the three doses under the supervision of a healthcare provider
1.4	Effective Date: 10/07/2021	For asthma indication: Updated LABA and LAMA requirement to LABA or LAMA

1.3	Effective Date: 08/12/2021	Criteria updated – Self-administration after three doses provided under the guidance a healthcare provider to apply to all indications.
1.2	Effective Date: 06/10/2021	Policy update to include criteria for asthma and self administration of Xolair. The criteria for asthma was previously part of the Biologics for Asthma Policy which will be retired
1.1	Effective Date: 02/04/2021	Policy update to include nasal polyp indication and related criteria
1.0	Effective Date: 01/01/2021	New Policy

Omvoh™ IV (mirikizumab-mrkz)
HCPCS: J2267

Background Information:

- Omvoh is an interleukin (IL)-23 antagonist that selectively binds the p19 subunit of IL-23 and is indicated for the treatment of moderately to severely active UC and moderately to severely active CD in adults.

- UC and CD are two of the most common forms of inflammatory bowel disease (IBD). Both UC and CD are chronic, relapsing, remitting, inflammatory conditions of the gastrointestinal (GI) tract. UC only involves the large intestine as opposed to CD, which can affect any part of the GI tract from mouth to anus. CD can also affect the entire thickness of the bowel wall, while UC only involves the innermost lining of the large intestine. UC can present with symptoms of abdominal discomfort or loose bowel movements, including blood. The cause of UC or CD is not fully understood; however, research suggests that an interplay between environmental factors, genetics, and intestinal microbiota may contribute to the development of UC or CD. UC has an incidence of 9 to 20 cases per 100,000 persons per year. Its prevalence is 156 to 291 cases per 100,000 persons per year.

- The 2019 American College of Gastroenterology (ACG) guidelines and the 2020 American Gastroenterology Association (AGA) guidelines state therapeutic management in UC should be guided by the specific diagnosis, an assessment of disease activity, and disease prognosis. Treatment selection should be based not only on inflammatory activity but also on disease prognosis. Remission can be induced using a variety of medications, including oral 5-aminosalycylic acid (5-ASA), corticosteroids, or biologic agents. Thiopurines, such as azathioprine and mercaptopurine, can be used to maintain remission. The tumor necrosis factor inhibitor (TNFi) agents infliximab, adalimumab, and golimumab are effective for treatment of patients with UC. Treatment guidelines do not recommend the use of one agent over another as there have been no head-to-head trials comparing the agents to one another. Vedolizumab is another guideline recommended option in patients with moderately to severely active UC for induction of remission, and in patients with moderately to severely active UC who have previously failed anti-TNF therapy, for induction of remission. Sphingosine 1-phosphate (S1P) receptor modulators have not been included in these guidelines.

- The 2018 ACG guidelines establish therapeutic recommendations for patients with CD based upon disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Current therapeutic approaches should be considered a sequential continuum to treat acute disease or induce clinical remission and then to maintain response/remission. In general, clinical evidence of improvement should be evident within 2 – 4 weeks and the maximal improvement should occur within 12 – 16 weeks. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease, have their medication dose adjusted in order to attempt to optimize therapy, or advance to treatment for moderate to severe disease according to their clinical status.

- Corticosteroids are used primarily for the treatment of flares of CD. Conventional corticosteroids are effective for reducing the signs and symptoms of active CD and induction of remission in patients with moderately to severely active CD. Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active disease. The ACG guidelines recommend prednisone equivalent doses ranging from 40 to 60 mg per day. These doses are typically maintained for 1 –2 weeks and tapered at 5 mg weekly until 20 mg and then 2.5 –5 mg weekly. Once begun, care should be taken to ensure that corticosteroids are successfully discontinued, and steroid-sparing agents should be used.

- In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, mercaptopurine, azathioprine, and intramuscular or subcutaneous methotrexate are effective steroid-sparing agents and guideline recommended. Maximum effectiveness of these agents can be seen between 8 to 12 weeks from therapy initiation. Methotrexate is also recommended in combination with steroids as effective for treatment of moderately active steroid-dependent/resistant CD. Cyclosporine, tacrolimus, and mycophenolate are not recommended for treatment of CD.

- Biologics, such as TNFi are recommended to treat CD that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. The ACG guidelines also recommend the use of biologics in combination with immunosuppressants to help decrease the formation of antibodies against the biologic therapy. There are no robust, published studies to support use of biologic agents in combination.

- The 2021 AGA guidelines include similar recommendations for the management of moderate-to-severe CD compared to the recommendations cited in the 2018 ACG guidelines. Both guidelines recommend corticosteroids over no treatment for induction of remission. Additionally, both guidelines recommend thiopurines, such as azathioprine or 6-mercaptopurine, as steroid-sparing agents for maintenance of remission. The AGA guidelines also recommend the same biologic agents cited in the ACG guidelines for treatment of CD, with the exception of Tysabri® (natalizumab), which the ACG suggests against use of due to its associated risk of progressive multifocal leukoencephalopathy (PML).

- Of note, the AGA guidelines conditionally recommend earlier introduction of biologic therapy prior to failure of corticosteroids; however, this recommendation is supported by a low level of clinical evidence. To date, no blinded randomized controlled trials (RCTs) have demonstrated the superiority of early introduction of biologic therapy compared to conventional induction therapy with corticosteroids followed by steroid-sparing therapy. The 2021 AGA guideline authors also acknowledge that earlier therapy with either combination immunomodulator plus biologic therapy or biologic monotherapy may result in over-treating some patients and potentially exposing them to treatment-related risks and costs with limited benefit.

- The efficacy of Omvoh for UC was based on results from the LUCENT program, which included two randomized, double-blind, placebo-controlled Phase III clinical trials consisting of one 12-week induction study (UC-1) and one 40-week maintenance study (UC-2) for 52 weeks of continuous treatment. All patients in the LUCENT program were required to have had an inadequate response to, loss of response to, or inability to take one or more glucocorticoids or immunomodulators for the treatment of UC (i.e., conventional treatment failure), or biologic

therapy or a Janus kinase (JAK) inhibitor for the treatment of UC (i.e., treatment failure with biologic agent or tofacitinib). Patients were allowed to receive oral 5-ASA, oral glucocorticoids, azathioprine, 6-mercaptopurine, or methotrexate at stable doses throughout the trial.

- The primary endpoint of UC-1 and UC-2 was clinical remission at Week 12 and Week 52, respectively. The secondary endpoints of UC-1 were clinical response, endoscopic improvement, and histologic-endoscopic mucosal improvement (HEMI) at 12 weeks. The secondary endpoints of UC-2 were endoscopic improvement, maintenance of clinical remission in subjects who achieved clinical remission at 12 weeks, corticosteroid-free clinical remission, and HEMI at 40 weeks (a total of 52 weeks of treatment).
    - Of patients treated with Omvoh at 12 weeks in UC-1:
        - 24% achieved clinical remission compared to 15% with placebo ($p<0.001$).
        - 65% achieved a clinical response compared to 43% with placebo ($p<0.001$).
        - 34% achieved endoscopic improvement compared to 21% with placebo ($p<0.001$).
        - 25% achieved histologic-endoscopic mucosal improvement compared to 14% with placebo ($p<0.001$).
        - Of patients treated with Omvoh at 40 weeks (a total of 52 weeks of treatment) in UC-2:
        - 51% achieved clinical remission compared to 27% with placebo ($p<0.001$).
        - 50% achieved corticosteroid-free clinical remission compared to 27% with placebo ($p<0.001$). Patients in steroid-free remission stopped using corticosteroids for at least the previous 12 weeks prior to the one-year assessment.
        - 58% achieved endoscopic improvement compared to 30% with placebo ($p<0.001$).
        - 66% achieved maintenance of clinical remission in patients who achieved clinical remission at Week 12 compared to 40% with placebo ($p<0.001$).
        - 43% achieved histologic-endoscopic mucosal improvement compared to 22% with placebo ($p<0.001$).
- Clinical trials have not evaluated the safety and efficacy of Omvoh when used in combination with other biologics or targeted DMARDs.

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Policy History		
#	Date	Change Description
1.3	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Added criteria requiring member to self-administer unless clinically unable to do so
1.2	Effective Date: 04/10/2025	Updated to include new indication: Crohn's disease
1.1	Effective Date: 10/03/2024	Added "for the same indication" to the not to be used in combination with other biologics or targeted DMARDs criteria
1.0	Effective Date: 02/12/2024	New Policy

Onasemnogene abeparvovec Products
Itvisma (onasemnogene abeparvovec-brve) J3590
Zolgensma (onasemnogene abeparvovec) J3399

Background Information:

- Zolgensma is an AAV9 that works by replacing the missing or defective SMN1 gene with a functional copy that makes SMN protein and is indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.

- Itvisma is an AAV vector-based gene therapy indicated for the treatment of SMA in adult and pediatric patients 2 years of age and older with confirmed mutation in SMN1 gene.

- SMA is a severe, inherited progressive neuromuscular disease that causes devastating muscle atrophy and disease-related complications in approximately 4 to 10 per 100,000 live births. SMA is caused by a mutation in the SMN1 gene that results in a deficiency of SMN protein. People have a "backup" copy of this gene called SMN2 that produces low levels of SMN protein. SMA varies in severity with four different types that inversely correlates to the number of SMN2 copies a person has. The type of SMA a person has is based on function and age of onset. Type 1 is the most severe type of SMA and the most common, affecting 6 out of every 10 children with SMA. Those with Type 1 have the fewest number of SMN2 copies (usually 2 or fewer). Type 1 patients have an age of onset usually between 0-6 months, and as the natural history of those with Type 1 SMA progresses the children will never be able to sit unsupported. Untreated life expectancy of Type 1 patients is less than 2 years old. Type 2 patients usually present around 7-18 months of age and will have the ability to sit, but never stand. The majority of SMA Type 2 patients have 3 copies of SMN2. Type 3 SMA patients present after 18 months of age and usually are able to stand and walk. About 51% of the patients with SMA Type 3 have 3 copies of SMN2 while 46% have 4 copies of SMN2. Although there is an inverse correlation between severity of disease and number of SMN2 copies, diagnoses of type is not solely based on number of SMN2 copies.

- The diagnosis of SMA is based on molecular genetic testing. Genetic testing of SMN1/SMN2 is highly reliable and it is first line investigation when the condition is suspected in a typical case. In approximately 96% of patients, SMA is caused by homozygous absence of exons 7 and 8 of the SMN1 gene, or, in some cases, only of exon 7.

- SMA patients' motor function and ability are monitored in a variety of ways, including but not limited to Bayley Scales of Infant and Toddler development (BSID), Motor Function Measure 32 (MFM-32), Hammersmith Infant Neurological Exam (HINE), Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM) Test (non-ambulatory patients), Six-Minute Walk Test (6MWT) (ambulatory patients only) and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND).

- There is currently no data supporting co-administration of onasemnogene abeparvovec with other SMA therapies, or in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence).

- CureSMA developed a treatment algorithm published in 2018. In September 2019, the working group reconvened to update its stance on infants with 4 copies of SMN2 on newborn screening. The working group has updated their stance and recommends immediate treatment for infants diagnosed with SMA via newborn screening with 4 copies of SMN2. Zolgensma's pivotal STR1VE trial included patients with SMA Type 1 who had 2 copies of SMN2. Zolgensma's SPR1NT trial, an ongoing Phase III, open-label, single-arm, multi-center trial in presymptomatic patients is being studied in patients with either 2 or 3 copies of SMN2, and included one patient with four copies of SMN2. The RESTORE registry is an ongoing, prospective, multicenter, multinational, non-interventional observation study that is evaluating long-term outcomes in patients with SMA. This study included 4 patients with 4 copies of SMN2 and 5 patients with 4+ copies of SMN2 who received Zolgensma. The CHOP INTEND scores showed improvement from baseline in this subset of patients.

- The approval of Itvisma was based on efficacy results from the Phase III, randomized, double-blind STEER study, which included 136 patients aged 2 to 17 years old with SMA who were treatment-naïve and able to sit but never able to walk independently. Patients with elevated (reference to > 1:50) baseline serum anti-AAV9 antibody titer were excluded.

    - The primary endpoint was the change from baseline in Hammersmith Functional Motor Scale –Expanded (HFMSE) total score, which evaluates motor function in patients with SMA who have limited ambulation, comprising of 33 graded items that assess various motor skills ranging from sitting to using the stairs, at the end of follow-up, defined as the average of the Week 48 and Week 52 assessment, in Itvisma compared to sham.

        - Patients in the Itvisma group saw a mean change of 2.39 points in the HFMSE total score compared to 0.51 points in the sham group, a treatment difference of 1.88 points (p-value = 0.0074).

    - The Phase IIIb STRENGTH trial enrolled 27 patients 2 to 17 years of age who have discontinued treatment with Spinraza® and/or Evrysdi® (mean duration of prior treatment 4.32 years and 2.98 years, respectively). The findings in this trial demonstrated stabilization of SMA based on the HFMSE score for the overall study population over 52 weeks.

- In the clinical trials patients were required to have baseline anti-AAV9 antibody titers of ≤ 1:50, measured using an enzyme-linked immunosorbent assay (ELISA). Evidence of prior exposure to AAV9 was uncommon. The safety and efficacy of onasemnogene abeparvovec in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. Antibodies titers above 1:50 may inhibit the efficacy of gene therapy.

- Bridging therapy with either Evrysdi or Spinraza prior to the use of onasemnogene abeparvovec can be appropriate in young patients with elevated anti-AAV9 antibodies. Elevated titers are not common (~13%) in SMA patients. Those that do have titers can get it from the placenta at birth from mothers who have acquired them. Just like other maternal antibodies passed on to children, these antibodies diminish over time. Bridging therapy allows patients to start therapy without delay, and waits for the titers to naturally diminish. Scientists have stressed the importance of treating SMA as early as possible, and suggested that patients with elevated antibodies be given disease-modifying therapies that work through different mechanisms — Spinraza (nusinersen) or Evrysdi (risdiplam) — as "bridge treatments" until able to receive onasemnogene abeparvovec.

- Onasemnogene abeparvovec can increase liver enzyme levels and cause acute serious liver injury. Oral corticosteroid medication should be given one day before and for 30 days after infusion with onasemnogene abeparvovec to avoid liver injury.

- Provider portals are used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.9	Effective Date: 02/12/2026	Updated title from Zolgensma (onasemnogene abeparvovec-xioi) to Onasemnogene abeparvovec Products. Added Itvisma to policy Added criteria that the member has not received prior treatment with any gene therapy or are being considered for treatment with any other gene therapy for SMA
1.8	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.7	Effective Date: 08/08/2024	Updated criteria to specify that Zolgensma will not be used concurrently with Evrysdi/Spinraza due to a bridging scenario
1.6	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.5	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 06/09/2022	Updated criteria to allow for Zolgensma use in those with 4 or fewer copies of SMN2 to align with CureSMA guidelines
1.3	Effective Date: 04/08/2021	This policy replaces previously approved criteria that was embedded in a drug review which will be retired.
1.2	Effective Date: 08/13/2020	Annual review of criteria was performed, no changes were made.
1.1	Effective Date: 08/15/2019	New full drug review
1.0	Effective Date: 02/14/2019	New Policy

Onpattro® (patisiran)
HCPCS: J0222

Background Information:

- Transthyretin amyloidosis (ATTR) is a progressive, life-threatening disorder characterized by the deposition of amyloid fibrils composed of transthyretin (TTR), a plasma transport protein for thyroxine and vitamin A that is predominantly produced by the liver and to a lesser extent by the choroid plexus and in retinal cells.

- In ATTR, TTR misfolds, causing it to aggregate into amyloid fibrils that accumulate in organs, nerves, and tissues. The buildup of these amyloid deposits results in progressive dysfunction at the site of deposition. Amyloid deposition can occur in the heart, gastrointestinal tract, kidneys, thyroid, salivary glands, eyes, peripheral nervous system, and central nervous system. The phenotype is driven by deposition site and may be predominantly cardiac, neurologic, or mixed.

- There are two types of ATTR: hereditary (hATTR), or variant, which is due to inherited mutations of the TTR gene that cause misfolding of the tetramer subunits, and wild-type, which occurs in the presence of a normal TTR gene, is typically associated with aging, and is most often diagnosed in men 65 years and older. In wild-type ATTR, TTR typically only deposits in the heart and manifests as cardiac symptoms. hATTR, in contrast, may be predominantly neuropathic, cardiomyopathy, or a mixed phenotype characterized by both

- ATTR is the most common form of hereditary amyloidosis. Approximately 120 different mutations or gene deletions have been identified in the TTR gene, with Val30Met as the most prevalent in the world.

- hATTR with polyneuropathy (hATTR-PN) is the most common neurologic manifestation. Without treatment, patients will have progressive neuropathy and disability ultimately resulting in death within 10-15 years of disease onset.

- Patients with hATTR-PN may present with peripheral neuropathy (sensory and motor; tingling or increased pain in the hands, feet and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking), autonomic neuropathy (e.g., orthostasis, abnormal sweating, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety]), GI impairment, cardiomyopathy, nephropathy, or ocular deposition. Most hATTR-PN cases, however, are classified as neuropathic.

- Amyloid deposition induces a length-dependent peripheral neuropathy beginning in the lower limbs with symptoms like toe discomfort due to numbness and spontaneous pain. Continued aggregation of amyloid on the nerve fibers contributes to sensory loss extending upwards toward the proximal lower limbs as motor deficits and impaired sensations occur. Walking becomes increasingly difficult as balance and gait are

affected. Neuropathic pain transitions to a burning sensation worsening at night. Over time, sensory deficit extends to the upper limbs, forearms, fingers and trunk and motor deficit follows with the same length dependent progression. At this stage, potentially life-threatening autonomic dysfunction is present manifesting as orthostatic hypotension, anhidrosis, neurogenic bladder, disturbances of gastrointestinal motility, and sexual impotence.

- Cardiac disease may occur in approximately 50% of patients with hATTR-PN. Ocular involvement is also common, including vitreous opacity, dry eye, glaucoma, and pupillary disorder.

- A rarer presentation of hATTR is leptomeningeal and meningovascular amyloidosis, often with concomitant vitreous opacity (oculoleptomeningeal amyloidosis). A number of mutations have reportedly been linked to this type of hATTR, though it may also manifest in more advanced cases of Val30MET hATTR-PN.

    - Central nervous system symptoms include stroke, subarachnoid hemorrhage, dementia, ataxia, seizures, and sensorineural hearing loss.

    - The source of mutant TTR in (oculo)leptomeningeal and meningovascular amyloidosis is thought to be the choroid plexus and retinal cells versus the liver. As such, ocular and meningovascular manifestations are commonly seen after liver transplantation because the source of mutant TTR is left unaffected.

    - To date, no treatments have been proven to be beneficial for the treatment of (oculo)leptomeningeal and meningovascular amyloidosis.

- The 2013 guideline of transthyretin-related hereditary amyloidosis for clinicians recommends that the most reliable diagnostic approach involves genetic testing and tissue biopsy to confirm the presence of active amyloid formation. Genetic testing is needed to document the TTR gene mutations; if testing is normal, a diagnosis of hATTR is excluded.

- Options for treatment of hATTR are limited. Treatment strategies for hATTR include depletion of the source of mutant TTR, inhibiting TTR formation, stabilizing the TTR molecule from dissociating, and therapy directed at removing the amyloid deposits. Regardless of the choice of treatment, the 2013 guidelines and expert opinion from a panel of experts (2024) recommend initiation as soon as possible after diagnosis to slow or halt disease progression. The best outcomes have been shown in patients diagnosed at younger ages and/or without advanced disease.

- For hATTR-PN, our best treatment option historically had been orthoptic liver transplant, which removes the source of mutant TTR and was considered the gold standard for hATTR-PN treatment early in the course of disease. In hATTR-PN, the liver is the primary source of mutant TTR;

transplantation eliminates approximately 95% of the production of mutant TTR and may slow or halt disease progression outside of the brain and/or eyes, though nerve function rarely improves post-transplant. Transplant does not effectively prevent cardiomyopathy, however, and is not recommended for patients with late stage hATTR-PN or leptomeningeal disease. With later stages of hATTR-PN and cardiomyopathy, there are concerns of disease progression due to deposition of wild-type TTR from the transplanted liver on the preexisting amyloid from the variant TTR.

- Numerous disease-modifying therapeutics are now available for hATTR-PN, including Amvuttra (vutrisiran), Onpattro® (patisiran), and Wainua® (eplontersen). Guidelines have not yet been updated to include Amvuttra, Onpattro, and Wainua specifically; however, they do note that early detection is critical and patients with early-stage disease should be treated with any approved drugs as they become available and as the patient's disease state meets drug indications, independent of liver transplant plans.

- Amvuttra, Onpattro, and Wainua are FDA-approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Of these products, only Wainua is FDA approved to be administered by the patient or caregiver; a healthcare provider is required for administration of Amvuttra and Onpattro per the approved labeling. To date, there is no literature supporting the use of one product over another, nor is there support for the use of any of these products together or in combination with other therapies approved for ATTR (e.g., tafamidis [Vyndamax® and Vyndaqel®], acoramidis [Attruby®]). The 2024 expert opinion does not offer recommendations on choice of specific treatment due to the lack of direct comparison trials and advises that clinicians consider the efficacy and safety considerations, in addition to any comorbidities and personal preferences around ease of use for an individual patient.

- Onpattro is a small interfering ribonucleic acid agent (siRNA) targeting TTR. It works by silencing a portion of RNA involved in causing the disease. Onpattro is designed to deliver the drug directly into the liver to interfere with RNA production of an abnormal form of TTR. By preventing this, the drug can help reduce the accumulation of amyloid deposits in peripheral nerves.

    - In the pivotal phase 3 APOLLO trial, Onpattro demonstrated better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, numbness), reflexes and autonomic symptoms (blood pressure, heart rate, digestion) compared to those receiving the placebo infusions. Onpattro-treated patients also scored better on assessments of walking, nutritional status and the ability to perform activities of daily living.

- In clinical trials, Onpattro was only evaluated in patients with a baseline polyneuropathy disability (PND) score $\leq$IIIb, which equates to a familial amyloidotic polyneuropathy (FAP) stage of 1 or 2. The PND score (range 0-IV) stages disease based on walking ability, while the FAP stage (stage 0-3) assesses the patient's level of ambulation and the severity/progression of neuropathy. Onpattro was not evaluated in patients with baseline PND score of IV which, like FAP stage 3, designates patients with late-stage, significantly advanced disease who are wheelchair-bound or bedridden, therefore clinical trials do not support use in this patient population with advanced disease.

- Patients with a history of liver transplant were also excluded from clinical trials of Onpattro. There is no literature to support that patients who received a liver transplant would experience benefit from treatment with Onpattro as they would not be expected to produce mutated TTR post-transplant.

- Additionally, there are no published clinical trials evaluating safety or efficacy of Onpattro for the treatment of any condition other than polyneuropathy of hATTR, and data is limited on the effect of Onpattro on other end organ dysfunction related to the underlying amyloidosis (i.e. cardiovascular outcomes).

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Policy History		
#	Date	Change Description
1.5	Effective Date: 06/05/2025	Reworded diagnosis criteria for clarity to align with approved labeling Removed criteria preventing use with previous liver transplant to align with management for other ATTR therapies
1.4	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 08/10/2023	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 08/04/2022	Removed FDA approved indications criteria and updated bullet e to prevent combination use with any drug approved for ATTR
1.1	Effective Date: 10/07/2021	Annual review of criteria was performed, no changes were made.
1.0	Effective Date: 01/01/2021	New Policy

Orencia® (abatacept)
HCPCS: J0129

Background Information:

- Orencia is a biologic disease-modifying agent that functions as a selective T-cell costimulation blocker. It is approved to treat RA, JIA, PsA as monotherapy or concomitantly with DMARDs, and as prophylaxis for aGVHD, in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing HSCT from a matched or 1 allele-mismatched unrelated donor. Concomitant use with other potent immunosuppressants (including other biologics and targeted DMARDs like Janus kinase (JAK) inhibitors), however, is not recommended.

  - Orencia may be administered as a subcutaneous injection or an intravenous (IV) infusion for RA, JIA, and PSA and administered IV for prophylaxis of aGVHD. Of note, subcutaneous Orencia is indicated for children 2 years of age and older with JIA, whereas administration of Orencia as an IV infusion should only be used in children 6 years of age and older with JIA. Refer to the prescribing information for additional details

- Rheumatoid Arthritis

  - The 2021 American College of Rheumatology (ACR) Guidelines for the Treatment of Rheumatoid Arthritis (RA) established recommendations for the care of adult RA patients. The guidelines state that treatment decisions should follow a shared decision-making process and should be reevaluated within a minimum of 3 months based on the efficacy and tolerability of the DMARD(s) chosen.

  - For the initial treatment of symptomatic RA, the guidelines strongly recommend the use of conventional synthetic DMARD (csDMARD) monotherapy in those who are DMARD-naive. csDMARD monotherapy is a less costly first line treatment option with an extensive safety record accompanied by well-documented clinical efficacy and a large body of clinical experience and familiarity among prescribers. csDMARDs in the guidelines refer to methotrexate (MTX), hydroxychloroquine, leflunomide (LEF), and sulfasalazine. Azathioprine, cyclosporine, minocycline, and gold were not included due to their infrequent use in RA and lack of new data since the prior guidelines were published. Oral MTX is recommended as the preferred initial DMARD for patients with moderate-to-high disease activity, and hydroxychloroquine is recommended as the preferred initial DMARD for patients with low disease activity.

  - If disease activity remains moderate or high despite optimal dosing of methotrexate monotherapy, the use of dual therapy with methotrexate plus biologic DMARD (bDMARD; etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, sarilumab, rituximab) or targeted synthetic DMARD (tsDMARD; tofacitinib, baricitinib, upadacitinib) therapy is

conditionally recommended over the use of triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine). The guidelines do not inform preference of bDMARD over tsDMARD therapy, or vice-versa, for use in combination with MTX. No one agent has been shown to be superior to another. The guidelines do acknowledge the emergence of safety signals for the JAK inhibitor class (tsDMARD), and state that further modification of this recommendation may be necessary as additional data are published.

  - A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a pre-defined target (low disease activity or remission).

- Juvenile Idiopathic Arthritis

  - Juvenile idiopathic arthritis (JIA) defines a collection of inflammatory arthritides of unknown etiology. Onset is prior to 16 years of age with a minimum duration of 6 weeks and other potential causes of synovitis are excluded. JIA can be subdivided into polyarticular JIA and systemic JIA.

  - Polyarticular JIA (pJIA) is defined by the presence of more than 4 affected joints in the first 6 months of illness and comprises 20-30% of children with JIA. Therapy is directed toward treating the underlying inflammation and preventing JIA-associated complications and adverse effects of its treatment.

  - The 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF) guideline for the treatment of JIA strongly recommends initial therapy for pJIA with a DMARD such as MTX or LEF. MTX is conditionally recommended over LEF as it has a greater volume of data supporting its effectiveness compared to leflunomide and can be administered subcutaneously (recommended) or orally. The guidelines consider an adequate trial of a DMARD to be 3 months.

  - If moderate or high disease activity persists despite an adequate DMARD trial, the ACR/AF guidelines recommend biologic agents either in combination with a DMARD or as monotherapy in certain situations. Biologic agents FDA approved for pJIA in patients 2 years of age and older include Humira® (adalimumab), Enbrel® (etanercept), Actemra® (tocilizumab), Orencia (abatacept), Simponi Aria® (golimumab), Xeljanz® (tofacitinib), and Xeljanz (tofacitinib) oral solution.

- Of note, biologic therapy may be an appropriate initial therapy in pJIA patients with risk factors and involvement of high-risk joints, high disease activity, and/or for those judged to be at high risk of disabling joint damage.

- There is the most experience with tumor necrosis factor inhibitors (TNFi; Humira, Enbrel, Simponi Aria) as initial biologic therapy; however, the preferred class of initial biologic is not specified in the guideline recommendations due to a lack of comparative data and the consideration that non-TNFi biologics may be preferred in certain patient-specific scenarios. If a TNFi is started as the initial biologic, switching to a non-TNFi (tocilizumab or abatacept) is recommended over switching to a second TNFi. An exception to this is for those who had a good initial response to the first TNFi.

    - Psoriatic Arthritis

- Psoriatic Arthritis (PsA) is a chronic inflammatory disease often associated with psoriasis. Psoriasis is an autoimmune disease affecting the skin, resulting in scaly red and white patches. These patches, called plaques, may appear anywhere on the body. The inflammation may also develop in the joints, which is classified as PsA. PsA occurs in up to 30% of patients with psoriasis, most commonly appearing between the ages of 30 and 50. PsA causes pain, stiffness, and swelling in and around the joints. If not properly treated, progressive joint damage may occur.

- Per the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guideline for the treatment of psoriatic arthritis: All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.

- In treatment-naïve patients, oral systemic medications (OSMs), such as methotrexate, sulfasalazine, cyclosporine, and leflunomide, may be used in patients without severe psoriatic arthritis and without severe psoriasis. OSMs have robust longitudinal safety and efficacy data in patients with PsA. Maximal response to OSMs is most commonly achieved within 3 months of therapy.

- If PsA remains active despite OSM therapy, switching to a TNFi, an interleukin-17 inhibitor (IL-17i), or an IL-12/23i biologic is recommended over switching to a different OSM; switching to a TNFi biologic over an IL-17i or IL-12/23i biologic is conditionally recommended in this scenario based on moderate quality evidence. Additional treatment options include Orencia (abatacept) and Xeljanz (tofacitinib). The detailed recommendations for subsequent therapies can be found in the 2018 ACR/NPF guideline for the treatment of psoriatic arthritis.

    - Prophylaxis for Acute Graft vs. Host Disease

- Prophylaxis of aGVHD centers on immunosuppression of the donor cells, either pharmacologically or via T cell depletion. There is no agreed-upon standard regimen, and clinical practice varies by institution. Guidelines for GVHD prophylaxis have been proposed by the European Group for Blood and Marrow Transplantation (EBMT) and European LeukemiaNet (2020).

- According to the EBMT, the consensus recommendations for the prophylaxis of GVHD in allogenic transplantation with myeloablative conditions has the standard prophylaxis being cyclosporine plus a short course of methotrexate. Tacrolimus plus methotrexate is regarded as

equivalent, but experience in Europe is too limited to support recommendations. Antithymocyte globulin has been shown to reduce chronic GVHD and improve the quality of life in transplantations from an unrelated donor. Therefore, antithymocyte globulin can be included in the prophylaxis regimen for unrelated donor transplantations. GVHD prophylaxis for reduced intensity conditioning has the standard prophylaxis being cyclosporine plus mycophenolate mofetil. Orencia has not been included in the EBMT proposed guidelines.

- Donor selection for HSCT is a critical element contributing to the success of the transplant. Matching donor and recipient for human leukocyte antigen (HLA) class I (-A, -B, and -C) and class II (-DRB1 and -DQB1) haplotypes is a key part of successful allogeneic HSCT. Molecular typing, used for allele matching, defines HLA genes by their DNA sequences. Molecular typing is necessary for HLA matching in unrelated donor transplants. An 8 of 8 HLA match refers to donor-recipient pairs matched for HLA-A, HLA-B, HLA-C, and HLA-DRB1 at the allele level. A 7 of 8 HLA match refers to pairs with a single allele or antigen mismatch at either HLA-A, HLA-B, HLA-C, or HLA-DRB1. In the Study GVHD-1, participants were either in an 8 of 8 HLA-matched cohort or a 7 of 8 HLA-matched cohort.

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Policy History		
#	Date	Change Description
1.6	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Added criteria requiring member to self-administer unless clinically unable to do so
1.5	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.4	Effective Date:	Annual review of criteria was performed, no changes were made

	02/08/2024	
1.3	Effective Date: 02/02/2023	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 02/10/2022	Updated to include Orencia's new indication for prophylaxis of acute graft versus host disease
1.1	Effective Date: 12/09/2021	Removed FDA approved indication and the oral DMARD criteria for psoriatic arthritis.
1.0	Effective Date: 01/01/2021	New Policy

Oxlumo® (lumasiran)
HCPCS: J0224

Background Information:

- Primary hyperoxaluria (PH) is an ultra-rare genetic disease characterized by recurrent kidney and bladder stones. There are three types of PH that differ in their severity and underlying genetic mutation: PH1, PH2, and PH3. PH1 is the most common form of PH, accounting for around 80% of total cases and affecting approximately 3,000 to 5,000 patients in the US. PH1 patients have a mutation of the AGXT gene, which results in decreased or absent hepatic enzyme alanine-glyoxylate aminotransferase (AGT). AGT converts glyoxylate to glycine, causing an increase in glyoxylate and oxalate. The excess production of oxalate by the liver results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones, nephrocalcinosis, progression to kidney failure, and systemic organ dysfunction. PH1 can be suspected in patients with increased urinary oxalate excretion, indicated by levels >1 mmol/1.73 m^2 per day. Genetic testing for a mutation in the AGXT gene confirms the PH1 diagnosis.

- Prior to the approval of Oxlumo, high-dose vitamin B-6 (pyridoxine), a cofactor for the AGT enzyme, was the only treatment proven to target the underlying pathophysiology of PH1. In 30-50% of PH1 patients, vitamin B-6 reduces oxalate levels and prevents accumulation in the kidneys. Responsiveness to vitamin B-6 is defined as a >30% decrease in urinary oxalate excretion after a minimum trial period of 3-6 months at the maximum tolerated dose. Experts recommend a starting dose of 5 mg/kg/day, with a maximum daily dose of 20 mg/kg. 56% of patients in the clinical trials for Oxlumo received concomitant vitamin B-6. Sensory neurotoxicity is a rare, dose-limiting side effect of vitamin B-6.

- Hyperhydration is a common supportive measure for management of PH1. Increasing fluid intake to 3 L/m^2 body surface area (BSA) per day can create higher urinary output, which decreases tubular fluid oxalate concentration and intratubular deposition, thereby preventing oxalate accumulation in the kidney. Experts recommend this approach of increasing fluid intake to help manage PH1. Pediatric patients may require a gastronomy tube to meet the high daily fluid requirement. Potassium citrate (0.1 to 0.15 g/kg) can be used to decrease the amount of calcium oxalate. The citrate component will allow calcium citrate to form, which is much more soluble than calcium oxalate. Urinary pH must be kept between 6.2 and 6.8 to be alkaline.

- Oxlumo was the first FDA-approved medication indicated for the treatment of PH1 to lower urinary and plasma oxalate levels in pediatric and adult patients. Oxlumo is an RNA interference therapy that reduces levels of the glycolate oxidase (GO) enzyme by targeting mRNA in the hepatocytes. Decreased GO enzyme levels reduce the amount of available glyoxylate, which is the substrate for oxolate production. The GO enzyme is upstream from the deficient AGT enzyme that causes PH1; therefore, the mechanism of action of Oxlumo is independent of the underlying AGXT gene mutation.

- The approval of Oxlumo was based on three studies in patients with PH1: a randomized control trial in pediatric patients ages 6 years and older with PH1 (ILLUMINATE-A), a single-arm clinical trial in pediatric patients less than 6 years of age with PH1 (ILLUMINATE-B), and a single-arm clinical trial in pediatric and adult patients with PH1 with advanced chronic kidney disease, including those on hemodialysis (ILLUMINATE-C). Of

note, the ILLUMINATE-A and ILLUMINATE-B trials excluded patients with systemic oxalosis, eGFR <30-45 mL/min, undergoing dialysis, or a history of kidney and liver transplants. ILLUMINATE-C did not exclude patients with eGFR <30 mL/min or those undergoing hemodialysis, and trial results support the efficacy of Oxlumo in PH1 patients with advanced renal disease. Of note, patients undergoing peritoneal dialysis and those with history of kidney or liver transplants were excluded from ILLUMINATE-C.

- The first trial, ILLUMINATE-A, was a placebo-controlled, double blind randomized controlled trial including patients 6 to 61 years old. 26 patients received Oxlumo and 13 received placebo. The primary endpoint was percent reduction from baseline in 24-hour urinary oxalate excretion (corrected for BSA) in months 3 to 6 of the trial. The least squares mean percent change was -65% (95% CI: -71, -59) in the Oxlumo group and -12% (95% CI: -20, -4) in the placebo group. By 6 months, 52% of patients receiving Oxlumo achieved normal 24-hour urinary oxalate, compared to 0% of patients receiving placebo.

- The second trial, ILLUMINATE-B, was a single-arm study. 16 patients younger than six years of age received Oxlumo. Using another measure of oxalate in the urine, the study showed, on average, a 71% (95% CI: 65, 77) decrease in urinary oxalate by the sixth month of the study.

- The third trial, ILLUMINATE-C, was a single-arm study that assessed the efficacy of Oxlumo in patients with PH1 with advanced renal disease (eGFR <30mL/min or those receiving hemodialysis). 21 patients aged 0 months and older (range: 0-59 years) received Oxlumo. Using the measure of oxalate in the plasma, the study showed on average a 33% (95% CI: -15, 82) and 42% (95% CI: 34, 51) reduction in plasma oxalate at month 6 compared to baseline, respectively, for patients not receiving hemodialysis at enrollment (Cohort A, N=6) and for patients receiving hemodialysis at enrollment (Cohort B, N=15). Additionally, at 6 months, no patients demonstrated worsening of nephrocalcinosis grade, 2 patients demonstrated no change in nephrocalcinosis grade, and 5 patients demonstrated improvement in nephrocalcinosis grade compared to baseline.

- Rivfloza™ was the 2nd FDA approved medication for the treatment of PH1. Rivfloza is a small interfering ribonucleic acid (siRNA) that inhibits the production of the hepatic lactase dehydrogenase (LDH) enzyme – an enzyme that is involved in the conversion of glyoxylate to oxalate. Rivfloza is approved to lower urinary oxalate levels in children 2 years of age and older and adults with PH1 and relatively preserved kidney function, e.g., eGFR ≥ 30 ml/min/1.73 m^2. In addition, Rivfloza is approved for both self-administration and healthcare provider administration.

- Clinical trials showed that Oxlumo and Rivfloza can effectively treat the underlying pathophysiology of oxalate overproduction. Data to show that Oxlumo or Rivfloza delays or precludes the need for liver and/or kidney transplantation is forthcoming and will impact these therapies prospective value.

  - Systemic oxalosis is defined as the spread of oxalate to organs outside of the kidneys, such as the joints, skin, bones, and heart. This can lead to organ dysfunction and death. The ILLUMINATE-C trial established the efficacy of Oxlumo in patients with advanced PH1, including those with systemic oxalosis and those undergoing hemodialysis. One registry study found that around 40% of patients present with end-stage renal disease (ESRD) at the time of PH1 diagnosis, representing a significant proportion of the PH1 patient population.

- In patients with PH1, aggressive hemodialysis is indicated once plasma oxalate levels exceed 30 mmol/L to prevent systemic oxalosis. Patients with PH1 and advanced renal disease carry a higher risk for systemic oxalosis, as renal excretion of oxalate is greatly reduced as eGFR declines, leading to an increase in plasma oxalate levels. Peritoneal dialysis alone does not achieve sufficient oxalate clearance; however, peritoneal dialysis in combination with hemodialysis may be necessary for those who do not respond to hemodialysis alone. Patients receiving peritoneal dialysis either alone or in combination with hemodialysis were excluded from ILLUMINATE-C.

- Dialysis is often used as a bridge to future liver and/or kidney transplantation in patients with PH1. Patients with a history of liver and/or kidney transplantation were excluded from all Oxlumo and Rivfloza trials, as removal of the patient's native liver is considered curative by removing the source of oxalate overproduction. Subsequent kidney transplantation or simultaneous liver-kidney transplantation may be required for those with ESRD. The role of transplantation in the setting of PH1 may change in the future with the introduction of small-interfering RNA therapies such as Oxlumo and Rivfloza. However, additional long-term data is needed to understand whether these therapies can delay or eliminate the need for liver and/or kidney transplantation in patients with PH1.

- In 2023, OxalEurope and European Rare Kidney Disease Reference Network (ERKNet) released clinical practice recommendations for primary hyperoxaluria: an expert consensus statement. The highlights of these recommendations include:

  - Recommendation of generic testing of each patient with high clinical and/or biochemical suspicion of PH (A: strong recommendation).

  - Conservative treatment is recommended promptly in all patients with suspected PH (B: strong recommendation). Conservative treatment includes starting hyperhydration (3.5-4 l/day in adults, 2-3 l/m2 BSA in children, to be consumed throughout 24 hours) in all patients with suspected PH and preserved kidney function (A-B: strong recommendation). They recommend oral administration of potassium citrate (0.1–0.15 g/kg) in patients with preserved kidney function (C – moderate recommendation). In addition, they recommend testing pyridoxine responsiveness in all patients with PH1 and titrating its dose based on urinary oxalate excretion (A: strong recommendation). They also recommend that all patients with PH1 are tested for pyridoxine responsiveness; urine oxalate measurements should be repeated on at least two occasions after at least 2 weeks of pyridoxine administration for evaluation of pyridoxine responsiveness, defined as a mean decrease of >30% between the two samples.

  - RNAi therapy is recommended under a multitude of conditions including:

    - PH1 is genetically established AND

    - Pyridoxine unresponsiveness or partial responsiveness is biochemically established OR have a mutation consistent with pyridoxine unresponsiveness

- Urine oxalate excretion is > 1.5 times the upper reference limit AND

- Patients demonstrate a clinical phenotype of PH1, characterized by active stone disease AND/OR nephrocalcinosis AND/OR renal impairment (B: moderate recommendation) OR patients have no ongoing clinical disease (C: weak recommendation).

- No studies have been done using Oxlumo and Rivfloza in combination. Patients were excluded from the Rivfloza PHYOX2 clinical trial if they had use of an RNAi drug within the last 6 months.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 12/04/2025	Annual review completed, no changes to criteria. Added ERKNet/OxalEurope clinical practice recommendations.
1.3	Effective Date: 12/12/2024	Annual review completed, no changes to criteria
1.2	Effective Date: 12/14/2023	Updated to remove prescriber requirements and add criteria to not allow for use of Oxlumo in combination with Rivfloza
1.1	Effective Date: 06/08/2023	Hyperhydration criterion removed for patients based on ILLUMINATE-C study results
1.0	Effective Date: 05/01/2023	New policy

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors
Leqvio® (inclisiran) J1306

Background Information:

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein that targets LDL receptors for degradation and reduces the liver's ability to remove circulating LDL from the blood. Elevated levels of circulating PCSK9 are associated with elevated levels of low-density lipoprotein cholesterol (LDL-C) and consequently worsened cardiovascular outcomes. Inhibitors of PCSK9 bind to circulating PCSK9 and prevent it from binding to and degrading LDL receptors on the liver surface, resulting in more LDL receptors to remove circulating LDL from the blood.

- The first two fully human monoclonal antibodies to PCSK9 to have been approved by the FDA to treat patients with inadequately treated levels of LDL-C were Repatha (evolocumab) and Praluent (alirocumab). Both work by binding to circulating PCSK9 and preventing it from binding to and degrading LDL receptors on the liver surface, resulting in more LDL receptors to remove circulating LDL from the blood. Praluent and Repatha have been shown to lower LDL-C by up to 60% in patients on concurrent statin therapy and additionally have demonstrated cardiovascular outcomes benefits. Both products are approved for the following indications:

    - To reduce the risk of major adverse cardiovascular events (e.g., stroke, myocardial infarction, unstable angina) in adults at increased risk for these events with established cardiovascular disease

    - As an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, heterozygous familial hypercholesterolemia (HeFH), and homozygous familial hypercholesterolemia

        - Repatha is also approved for pediatric patients 10 years of age and older with HeFH, and Praluent for pediatric patients 8 years of age and older with HeFH

        - Repatha is also approved for use in pediatric patients 10 years of age and older with HoFH. Praluent lacks a pediatric indication HoFH.

- The most recent additions to the PCSK9 inhibitor class are Leqvio (inclisiran), the first small interfering RNA (siRNA) therapy directed to PCSK9 mRNA, and Lerochol (lerodalcibep-liga),a recombinant fusion protein that binds PCSK9. Both have been approved as an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, including HeFH.

- Unlike Praluent and Repatha, Leqvio utilizes the RNA interference mechanism to inhibit hepatic synthesis of PCSK9. In doing so, LDL receptor recycling and expression on the liver surface increase, thereby increasing LDL-C uptake by hepatocytes and consequently lowering the levels in circulation. In clinical trials Leqvio has demonstrated comparable LDL-C lowering potency to Praluent and Repatha. Leqvio's effect on

cardiovascular outcomes has yet to be determined. The ORION-4 and CITORION-2P cardiovascular outcomes trials with Leqvio are underway and expected to be completed in 2026 and 2027, respectively; results are expected to be comparable to Praluent and Repatha.

- All four products are administered as subcutaneous injections. With regard to administration and dosing frequency Praluent and Repatha are similar; both products can be self-administered and are dosed every two weeks or every month. Lerochol is self-administered once every month via subcutaneous injection via a single small-volume injection with extended room temperature stability. Leqvio, however, is intended for administration by a healthcare professional only and is administered every six months after an initial dose titration. Less frequent dosing and a required office visit could potentially yield better adherence with Leqvio compared to the self-administered alternatives.

- Combination use of more than one PCSK9 inhibitor has not been evaluated, and in clinical trials for Leqvio patients who were taking Praluent and/or Repatha were excluded from participating. Therefore, the use of any of the PCSK9 inhibitors in combination is not supported by evidence.

- The American College of Cardiology (ACC) at present in their 2022 Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering prefers PCSK9 monoclonal antibodies (i.e., Repatha, Praluent) as the initial PCSK9 inhibitor of choice in light of the demonstrated efficacy, safety, and cardiovascular outcomes benefits seen in the FOURIER and ODYSSEY Outcomes trials; however, those with poor adherence to PCSK9 monoclonal antibodies, adverse effects from PCSK9 monoclonal antibodies, or those unable to self-inject may be considered for use of Leqvio. Use of the product(s) with the lowest net cost provides the greatest value.

- Patients with clinical atherosclerotic cardiovascular disease (ASCVD) include those with a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD (including aortic aneurysm), all of atherosclerotic origin. These patients with established cardiovascular disease are at high risk of a cardiovascular disease event. Those with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions (i.e. age $\geq$ 65 years old, HeFH, diabetes mellitus, hypertension, chronic kidney disease, current smoking, LDL-C $\geq$ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe, history of congestive heart failure, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)) are considered very-high risk for future ASCVD events. Therapy to reduce the risk of subsequent events is known as secondary prevention.

- Patients presenting with severe primary hypercholesterolemia (LDL $\geq$ 190 mg/dL), including those with familial hypercholesterolemia (FH), have a high risk of ASCVD and premature/recurrent coronary events. Regardless of whether LDL-C levels $\geq$ 190 mg/dL are found to have a genetic mutation associated with FH, those patients with very high LDL-C are most likely to achieve the greatest benefit both in LDL-C reduction and ASCVD risk reduction from evidence based LDL-C-Lowering therapy.

- FH is an autosomal dominant genetic disease caused by functional mutations in the LDLR, APOB, or PCSK9 genes, and is characterized by lifelong elevations of LDL-C that if left untreated leads to early-onset atherosclerosis and risk of cardiovascular events. Mutations in the LDLR gene are the most common causes of FH, accounting for 85%-90% of genetically confirmed cases. Diagnosis of FH should be considered in children presenting with persistently elevated LDL-C > 160 mg/dL, adults with LDL-C >190 mg/dL, and in all patients with early coronary artery disease. In the absence of confirmatory genetic testing, FH can be diagnosed using clinical criteria; commonly used diagnostic tools for the diagnosis of FH include the US Make Early Diagnosis to Prevent early Death (MEDPED) criteria, the UK Simon Broome system, and the Dutch Lipid Clinic Network criteria. Though the tools differ from one another, their predictive values are comparable.

- The incidence of HeFH in the United States is approximately 1 in 500. The Dutch Lipid Clinic Network criteria provide the most detailed assessment of the likelihood of a diagnosis of HeFH and includes the following parameters to confirm diagnosis:
    - An untreated LDL of $\geq$ 190 mg/dL (or $\geq$ 160 mg/dL in patients under 16 years of age) and at least one of the following:
        - Family history of a first or second degree relative with FH.
        - Family history of tendinous xanthoma(s) in 1st or 2nd degree relative and/or arcus cornealis in 1st degree relative
        - History of 1st degree relative with known premature coronary and vascular disease (i.e., < 55 years old in men, and < 60 years old in women)
        - Physical signs of FH such as the presence of tendon xanthomas in the patient, premature corneal arcus, premature tuberous xanthomas, or premature xanthelasma.
        - Presence of a mutation causing FH by DNA testing (e.g. mutation in LDLR, APOB, PCSK9).
- The UK Simon Broome System criteria differs from the Dutch Lipid Clinic Network in that the presence of a positive genetic test alone is sufficient to definitively diagnose familial hypercholesterolemia. Additional parameters to aid in the diagnosis of HeFH under the Simon Broome system include an LDL > 190 mg/dL and at least one of the following:
    - Tendon xanthoma in the patient or a 1st or 2nd degree relative
    - Presence of mutations in the LDLR, APOB, or PCSK9 gene
    - Family history of MI in a 2nd degree relative under 50 years old or a 1st degree relative under 60 years old
    - Family history of total cholesterol > 290 mg/dL in a 1st or 2nd degree relative.

- HoFH is ultra-rare affecting approximately 1,300 patients in the United States. Genetic mutations primarily affect the LDLR gene, resulting in virtually absent or impaired receptor-mediated catabolism of LDL-C and leading to severely elevated LDL-C levels (> 400 mg/dL) and a lack of responsiveness to standard lipid-lowering therapies. Diagnosis can be made via genetic testing for causative mutations in the LRLR, APOB, and PCSK9 genes, or clinically in patients with an untreated LDL-C of >500 mg/dL (or treated LDL-C ≥ 300 mg/dL) and one of the following: cutaneous or tendon xanthoma prior to 10 years of age, or elevated LDL-C levels in both parents consistent with HeFH. Untreated LDL-C < 500 mg/dL may be present in some patients with HoFH, particularly in young children, and would warrant genetic testing to clarify or confirm diagnosis. More recently, a rare autosomal recessive form of FH has been identified that is caused by mutations in the LDLRAP1 (also known as the ARH) gene. Though coined autosomal recessive hypercholesterolemia, this condition is considered as a form of HoFH and should be treated as such.

- LDL-C is a primary cause of atherosclerosis and a major risk factor for ASCVD. Randomized controlled trials of cholesterol lowering therapies have consistently demonstrated that LDL-C lowering reduces the risk of ASCVD. Generally speaking, lowering LDL-C levels by 1% yields an approximately 1% reduction in ASCVD risk, though this percent risk reduction may be slightly more or less at higher and lower baseline LDL-C levels, respectively.

- Statins are the cornerstone of pharmacologic therapy for lowering LDL-C both as primary and secondary ASCVD prevention. Statin therapy is divided into three categories by intensity, with atorvastatin, rosuvastatin, and simvastatin being the primary statin medications used in clinical practice.

	High Intensity	**Moderate Intensity**	**Low Intensity**
LDL-C Lowering	≥ 50%	30-49%	<30%
Statins**	Atorvastatin° 40mg, 80mg Rosuvastatin* 20mg, 40mg	Atorvastatin° 10mg, 20mg Rosuvastatin* 5mg, 10mg Simvastatin° 20-40mg Pravastatin* 40mg, 80mg Lovastatin° 40mg, 80mg Fluvastatin° XL 80mg Fluvastatin° 40mg BID Pitavastatin° 1-4mg	Simvastatin° 10mg Pravastatin* 10-20mg Lovastatin° 20mg Fluvastatin° 20-40mg

*Hydrophilic statin °Lipophilic statin	**Hydrophilic statins have greater hepatoselectivity and less influence on smooth muscle proliferation than lipophilic statins, which diffuse nonselectively into extrahepatic tissues such as the muscle and may therefore be more likely to cause myopathy.

- The 2022 ACC Expert Consensus Decision on the Role of Nonstatin Therapies for LDL-C Lowering recommends treatment with a maximally tolerated statin to lower LDL-C by ≥ 50% to a goal LDL-C level of <55 mg/dL for secondary prevention of ASCVD or <70 mg/dL for adults without clinical ASCVD and with severe hypercholesterolemia, including FH. Treatment with high-intensity or maximally tolerated statins has demonstrated reduced ASCVD risk in both primary and secondary prevention trials, in addition to reduced risk of myocardial infarction, coronary heart disease, and all-cause death with phenotypically or genetically confirmed FH. Peak changes in LDL-C levels are generally seen between 4 and 12 weeks after initiating therapy.

- If with a high-intensity statin the patient experiences statin-associated side effects that are not severe (e.g., myalgias), the statin dose can be reduced or alternate statins can be trialed with the ultimate goal of treating with a guideline-recommended maximally tolerated statin.

    - There are a variety of generically available statins that can be dosed at different intensities or dosing regimens to help mitigate bothersome side effects; therefore, it is reasonable to require a trial of at least two statins in patients experiencing statin-associated side effects.

    - Patients who experience more severe side effects with statin therapy (e.g. rhabdomyolysis) or recurrent statin-associated muscle symptoms despite multiple statin rechallenge attempts may need to discontinue statin use and transition to non-statin therapy that has been shown to provide clinical benefit.

- If maximally tolerated statin therapy fails to reduce LDL-C by at least 50% and/or the LDL-C level remains above goal, the 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-C lowering recommends considering adding either ezetimibe or a PCSK9 monoclonal antibody as the initial non-statin therapy. Preference of which agent to add may be influenced by the desired amount of LDL-C-lowering. ACC/AHA guidelines suggest that additional ASCVD risk reduction can be derived by adding ezetimibe to statin therapy, which can lower LDL-C by an additional 13-20%, and placebo-controlled randomized clinical trials have demonstrated favorable safety profiles and additional LDL-C reduction ranging from 43-64% with PCSK9 inhibitors in patients on maximally tolerated statin therapy. If additional LDL-C lowering is required after addition of a single non-statin agent (ezetimibe or PCSK9 monoclonal antibody) to statin therapy, a second evidence-based non-statin agent should be considered (e.g., ezetimibe + PCSK9 monoclonal antibody).

- If additional LDL-C lowering is warranted despite maximally tolerated statin therapy, ezetimibe, and a PSK9 monoclonal antibody, the addition of bempedoic acid may be considered, or the PCSK9 monoclonal antibody may be replaced with inclisiran. There is no cardiovascular outcomes data available at this time for inclisiran. For persistent severe hypercholesterolemia where drug therapy fails to adequately control LDL-C, such as in the case of HoFH, specialized therapies such as evinacumab, lomitapide, or LDL apheresis may be necessary to control LDL-C and referral to a

lipid specialist may be indicated. Of note, the safety and efficacy of the concurrent use of lomitapide with PCSK9 inhibitors like Repatha and Praluent for the treatment of HoFH has not been established.

- For children and adolescents 10 years of age and older with an LDL-C $\geq$ 190 mg/dL or $\geq$ 160 mg/dL with a clinical presentation consistent with FH who fail to respond adequately to 3 to 6 months of lifestyle therapy, the 2018 guidelines suggest initiation of statin therapy. Statin treatment intensity in children is not specified in the guidelines as it should be individualized to the child based on the severity of hypercholesterolemia and the needs of the child/family. Use of non-statin therapies to further treat persistently elevated LDL-C in children is not addressed in the guidelines; however, for children with HoFH Repatha may be a reasonable next step for children and adolescents who require additional LDL-C lowering since it is approved by the FDA for use in pediatric patients 10 years of age and older with HoFH in combination with diet and other LDL-C lowering therapies. Praluent, however, is only approved for adult patients with HoFH.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 02/12/2026	Added Lerochol to the policy For Medicare benefit ASCVD, primary hyperlipidemia, and HeFH criteria: changed required LDL values while on a high intensity statin from > 70 mg/dL and > 100 mg/dL to >55 mg/dL and > 70 mg/dL, respectively For Medicare benefit HoFH criteria: removed requirement that requested drug not be used in combination with Juxtapid (lomitapide)
1.3	Effective Date: 12/04/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 12/12/2024	Added criteria for Praluent and Repatha specific to Medicare to the policy
1.1	Effective Date: 12/14/2023	Annual review of criteria performed; no changes were made
1.0	Effective Date: 05/01/2023	New Policy

PiaSky® (crovalimab-akkz)
HCPCS: J1307

Background Information:

- PiaSky is a complement C5 inhibitor indicated for the treatment of adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) and body weight of at least 40 kg.

- Paroxysmal nocturnal hemoglobinuria is a rare acquired hematopoietic stem cell disorder in which red blood cells undergo cell lysis prematurely mediated by the alternative pathway of complement (APC). PNH arises due to a somatic mutation of the PIGA gene whose protein product is a glycosyl transferase. Glycosyl transferase is part of the biosynthetic pathway that generates glycosyl phosphatidylinositol (GPI) that serves as an anchor for membrane bound proteins on hematopoietic lineage cells. The mutation in PIGA results in a lack of glycosyl transferase activity and near-complete or complete absence of expression of all proteins that are GPI-anchored, including the complement inhibitory proteins CD55 and CD59. The deficiency of CD55 and CD59 cause the complement-mediated intravascular hemolysis characteristic of PNH.

- Phenotypic mosaicism of the peripheral blood is a characteristic feature of PNH and is based on quantitative differences in complement sensitivity. Cell complement sensitivity is divided into 3 types. PNH type I cells are defined by having normal sensitivity to complement-mediated lysis. PNH type II cells are moderately complement sensitive or 2 - 4 times more sensitive than normal. Finally, PNH type III cells are markedly complement sensitive or 15 - 25 times more sensitive than normal. Complement sensitivity varies greatly from patient to patient depending on their unique phenotypic mosaicism. Erythrocyte phenotype is clinically relevant as patients with primarily type II cells have a relatively benign clinical course. In contrast, those who have more type III cells, which are completely deficient in CD55 and CD59, will have a more severe clinical course due to increased complement-mediated hemolysis. There is no guideline recommended cutoff for when PNH can be diagnosed based on percentage of PNH type III cells.

- For patients with high disease activity, PNH complications increase significantly. High disease activity is defined as an elevated LDH greater than or equal to 1.5 times the upper limit of normal with constitutional symptoms of weakness, fatigue, hemoglobinuria, abdominal pain, dyspnea, hemoglobin less than 10 g/dL, dysphagia, and erectile dysfunction. Patients with an elevated LDH and at least one additional symptom should begin treatment with Piasky.

- Thrombolytic complications are the leading cause of morbidity and mortality in PNH. Acute thrombotic events require anticoagulation with heparin. If there is no contraindication, anticoagulation should continue indefinitely for a patient with PNH who has experienced a thromboembolic complication. Piasky should be initiated if a patient has experienced a thrombotic vascular event. For patients being treated

with Piasky and no history of thromboembolic complications, prophylactic anticoagulation may be unnecessary, although it is recommended that anticoagulation continue for those patients who experienced a thromboembolic event prior to initiating therapy with Piasky.

- PiaSky has been shown to decrease the number of blood transfusions required by patients and stabilize hemoglobin levels. It has been studied in patients with no transfusions in the 12 months prior to starting therapy, however, the median number of packed red blood cell (pRBC) units transfused in the 12 months prior to screening was 3.8 units.

- PiaSky has not been studied and there is no data to support use in combination with other medications used to treat PNH, such as, Ultomiris. However, for patients switching from Soliris or Ultomiris, Piasky's first intravenous loading dose should be administered no sooner than the time of the next scheduled complement inhibitor dose.

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Policy History		
#	Date	Change Description

1.1	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 10/01/2024	New Policy

Pulmonary Arterial Hypertension Products
Flolan® (epoprostenol) J1325
Remodulin® (treprostinil) J3285
Tyvaso® (treprostinil) J7686
Uptravi® (selexipag) J3490
Veletri® (epoprostenol) J1325
Winrevair™ (sotatercept-csrk) J3590

Background Information:

- FDA approved indications for medications covered in this policy:

    - Epoprostenol: A prostacyclin vasodilator indicated for the treatment of PAH (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.

    - Treprostinil: A prostacyclin vasodilator indicated for:

        -Treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).

        -Patients who require transition from epoprostenol, to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

    - Uptravi: A prostacyclin receptor agonist indicated for the treatment of PAH (WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH.

    - Winrevair: An activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events.

- CHEST 2019 guideline-supported therapies for WHO Functional Class II and III include: sildenafil, tadalafil, ambrisentan, bosentan, macitentan, riociguat, treprostinil inhalation, and iloprost inhalation.

- Additional CHEST 2019 guideline-supported therapies for WHO Functional Class III and IV include: epoprostinil IV and treprostinil IV/SQ, and in those who cannot use IV/SQ, treprostinil inhalation and iloprost inhalation.

- PDE5Is and ERAs are clinically effective guideline-supported therapies that have wide utility per CHEST guideline recommendations and are cost effective as they are available as generics.

- Opsumit (macitentan) has no clinical advantages over ambrisentan and bosentan at this time, as all three ERAs are now FDA approved to prevent disease progression and clinical worsening. Ambrisentan and bosentan are more cost effective therapies as they are available generically.

- CHEST 2019 guidelines suggest initial monotherapy with ERA, PDE5I, or Adempas (riociguat) for treatment of WHO Functional Class II or III, and suggest adding a second class if inadequate response to initial monotherapy.

- CHEST 2019 guidelines suggest adding a third drug class in WHO Class III or IV with deterioration.

- CHEST 2019 guidelines suggest inhaled prostacyclins (Tyvaso (treprostinil), Ventavis (iloprost)) for WHO Class III after failure of one or two classes of oral agents.

- The 2022 European Society of Cardiology (ESC) / European Respiratory Society (ERS) clinical guidelines recommend initial combination therapy of an ERA and a PDE5 inhibitor for patients with idiopathic PAH, heritable drug-associated PAH, or PAH-associated with connective tissue disease without cardiopulmonary comorbidities at low or intermediate risk.

- Cross benefit opportunities may exist to step on drugs on the medical benefit for prostacyclin drugs per guidelines, as SQ/IV therapy is preferred to inhalation for WHO Class III and WHO Class IV. Prostacyclin SQ/IV medications may be more cost-effective, however require more complex administration. Further investigation is warranted.

- Uptravi (selexipag) and Orenitram ER (treprostinil tablets) were found to have insufficient clinical evidence to support a guideline recommendation per the CHEST 2019 guidelines. Utilization of guideline supported agents is promoted by step therapy.

- Per package labeling, in Uptravi (selexipag) clinical trials at baseline, 80% of patients were being treated with a stable dose of an ERAs (15%), a PDE5Is (32%), or both (33%).

- Per FDA label, Adempas (riociguat) should not be used in combination with a PDE5I.

- Pulmonary hypertension (PH) with insterstitial lung disease and pulmonary fibrosis can be treated with IV or inhaled treprostinil. PDE5Is have shown little or no benefit in these patients. ERAs, specifically ambrisentan, have been shown to be ineffective and associated with adverse effects in patients with PH while bosentan and macitentan are ineffective in idiopathic pulmonary fibrosis (IPF) but have not been tested in IPF associated PH.

- Uptravi's prospective, multicenter, open-label, single-sequence, cross-over, Phase III study showed the safety, tolerability and pharmacokinetics of temporarily switching between oral Uptravi and Uptravi IV in 20 patients. Patients who were stable on oral Uptravi switched to IV Uptravi for three infusions including the morning and evening dose on Day 1, and morning dose of Day 2 before switching back to the oral formulation in the evening of Day 2.

- Winrevair's Phase III STELLAR trial showed improvement compared to placebo in the 6-minute talk distance of 41 meters at week 24. In this study most participants were receiving either three (61%) or two (35%) background drugs for PAH, and 40% were receiving prostacyclin infusions.

- Dosage modifications of Winrevair due to increased hemoglobin (Hgb) and decreased platelets may be necessary. Hgb and platelets should be checked before each dose for the first 5 doses, or longer if values are unstable, and should be monitored periodically thereafter. Winrevair is intended for use under the guidance of a healthcare professional. Patients and caregivers may administer Winrevair when considered appropriate and when they receive training and follow-up from the healthcare provider (HCP) on how to reconstitute, prepare, measure, and inject Winrevair. Clinical reasons a patient may be unable to self-administer Winrevair include but are not limited to:

- Patient or caregivers are unable to perform subcutaneous injections with proper technique

- Member requires monthly medical support from the physician

- Merck will be using two specialty pharmacies to dispense Winrevair in the United States: Accredo Health Group, Inc. and CVS Specialty. Merck has chosen this limited specialty pharmacy network to most efficiently provide access and support to patients. Accredo and CVS Specialty will be supporting patients and physicians by providing education and training for self-administration of Winrevair.

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Policy History		
#	Date	Change Description
1.7	Effective Date: 08/07/2025	Updated to include Yutrepia
1.6	Effective Date: 08/08/2024	Updated criteria for Tracleer suspension from “unable to swallow tablets” to t/f sildenafil or tadalafil AND ambrisentan or bosentan. Removed t/f sildenafil or tadalafil AND ambrisentan or bosentan criteria from Adempas.
1.5	Effective Date: 06/06/2024	Addition of Opsynvi and Winrevair Removed specific Opsumit criteria to reflect what is being implemented
1.4	Effective Date: 06/08/2023	Addition of Liqrev
1.3	Effective Date: 08/04/2022	Updated to add Tyvaso DPI formulation and Tadliq
1.2	Effective Date: 10/10/2021	Annual review of medical policy. Criteria applies to Medicare Part B only.

1.1	Effective Date: 06/10/2021	Updated policy with specific step therapy for certain medications following CHEST 2019 guidelines and included Tyvaso's new indication for PH-ILD; WHO Group 3
1.0	Effective Date: 01/01/2021	New Policy

Qalsody™ (tofersen)
HCPCS: J1304

Background Information:

- Qalsody is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the 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).

- ALS is the most common motor neuron disease in adults and is characterized by neurodegeneration of motor neurons in the brain and spinal cord. The incidence of ALS is approximately 1-2.6 cases per 100,000 persons annually, whereas the prevalence is approximately 6 cases per 100,000. The average age of onset of ALS is currently 58-60 years old and the average survival time from onset to death is 3-4 years. Mutations in the SOD1 gene account for approximately 2% of ALS cases (approximately 330 people in the US). In people with SOD1-ALS, mutations in their SOD1 gene cause their bodies to create a toxic misfolded form of SOD1 protein. This toxic protein causes motor neurons to degenerate, resulting in progressive muscle weakness, loss of function, and eventually, death.

- The American Academy of Neurology updated guidelines from 2009 (reaffirmed on January 11, 2020) titled "Update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies" recommend that riluzole should be offered to slow the disease progression in patients with ALS. The European Federation of Neurological Sciences (EFNS) guidelines on clinical management of amyotrophic lateral sclerosis (MALS)-revised report of an EFNS task force, from 2012 also recommend riluzole in all patients. Neither set of guidelines have been updated to include the two most recent ALS drug approvals: Radicava® or Relyvrio™. There are no therapies listed specifically for ALS with SOD1 gene mutations.

- The efficacy of Qalsody was assessed in the VALOR study, a Phase III, 28-week, randomized, double-blind, placebo-controlled clinical study in patients 23 to 78 years of age with weakness attributable to ALS and a SOD1 mutation confirmed by a central laboratory. One hundred eight (108) patients were randomized 2:1 to receive treatment with either Qalsody 100 mg (n=72) or placebo (n=36) for 24 weeks (3 loading doses followed by 5 maintenance doses). Concomitant riluzole and/or edaravone use was permitted for patients, and at baseline 62% of patients were taking riluzole and 8% of patients were taking edaravone. The non-modified intent to treat population had a slow vital capacity ≥ 50% of predicted value at baseline.

    - The trial showed a non-statistically significant 1.2-point difference in the Revised ALS Functional Rating Scale (ALSFRS-R) ($p = 0.97$).

    - Qalsody led to reductions in SOD1 by 35% compared to 2% for placebo and a 55% reduction in plasma neurofilament, a biomarker of neurodegeneration, compared to a 12% increase in the placebo-treated group.

- Additional analysis of the Phase III data combined with an open-label extension (OLE) study showed that earlier initiation of Qalsody slowed decline across measures of clinical and respiratory function, strength, and quality of life.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 08/07/2025	Updated to remove ALSFRS-R score requirements on initial, and to remove drugs specific renewal criteria and replace with standard renewal criteria.
1.3	Effective Date: 06/05/2025	Annual review of policy. No changes to criteria were made.
1.2	Effective Date: 06/06/2024	Annual review of policy. No changes to criteria were made.
1.1	Effective Date: 06/08/2023	New policy
1.0	Effective Date: 07/01/2023	New policy

Radicava® (edaravone)
HCPCS: J1301

Background Information:

- Radicava and Radicava ORS are indicated for the treatment of ALS

- ALS is a neurodegeneration disease characterized by rapid loss of upper and lower motor neurons, resulting in death by paralysis and respiratory failure usually within 24-48 months. It has been suggested that pathogenesis of neuronal degeneration in ALS may be unique in different individuals, which is one reason ALS research and development has had minimal advancements. One primary suggestion is that oxidative stress to motor neurons is largely responsible for the pathogenesis of ALS onset and progression.

- It is proposed that by reducing free radicals that cause oxidative stress on motor neurons, radical damage may be minimized, thus preventing progression of ALS. One primary tool to measure progression of ALS is called Revised ALS Functional Rating Scale (ALSFRS-R), which has been used in many clinical trials to determine treatment efficacy.

- The American Academy of Neurology updated guidelines from 2009 (reaffirmed on January 25, 2023) titled "Update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies" recommend that riluzole should be offered to slow the disease progression in patients with ALS. These guidelines have not been updated to include the most recent ALS drug approvals, including Radicava® or Qalsody™. The European Academy of Neurology (EAN) guideline on the management of amyotrophic lateral sclerosis in collaboration with European Reference Network for Neuromuscular Diseases (ERN EURO-NMD), which is an update of the 2012 European Federation of Neurological Societies guidelines strongly recommends lifelong riluzole at diagnosis, and to offer Qalsody (tofersen) as first-line for progressive ALS caused by pathogenic SOD1 mutations.

- Both guidelines recommend initiating riluzole as soon as possible after diagnosis along with non-pharmacotherapy. Non-pharmacotherapy goals are to maintain autonomy as long as possible through supportive care. The AAN recommends a multidisciplinary care approach that includes a neurologist when treating/caring for patients with ALS.

- The first of two Phase III trials failed to show significant difference between the treatment group and placebo in relativity to the ALSFRS-R score. Researchers determined that inclusion criteria (duration of disease within 3 years and forced vital capacity (FVC) at least 70%) had to be more stringent to observe responders. [Please see **Table 1** below for additional information regarding the trials].

- The second Phase III trial was conducted over 24 weeks and met a power of 80%. Based on the modified inclusion criteria (duration of disease within 2 years and FVC at least 80%), the trial concluded a significant difference in ALSFRS-R score between treatment group and placebo group.

- It is the Northeast Amyotrophic Lateral Sclerosis Consortum (NEALS) clinical investigators' opinion that a therapy that results in a change of 20-25% or greater in the slope of the ALSFRS-R would be considered clinically meaningful.

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Policy History		
#	Date	Change Description
1.7	Effective Date: 08/07/2025	Updated to remove ALSFRS-R score requirements on initial, and to remove drugs specific renewal criteria and replace with standard renewal criteria.
1.6	Effective Date: 02/13/2025	Annual review – no changes to the criteria were made.
1.5	Effective Date: 02/08/2024	Annual review – no changes to the criteria were made.
1.4	Effective Date: 02/02/2023	Updated FVC requirement to a vital capacity requirement
1.3	Effective Date: 12/01/2022	Updated renewal criteria to allow other clinical documentation outside of just patient assessments using the ALSFRS-R to determine if the medication is providing benefit
1.2	Effective Date: 08/04/2022	Update to include new oral suspension formulation Radicava ORS.
1.1	Effective Date: 08/12/2021	Annual Review
1.0	Effective Date: 01/01/2021	New Policy

Ranibizumab Policy
Byooviz™ (ranibizumab-nuna) Q5124
Cimerli™ (ranibizumab-eqrn) Q5128
Lucentis® (ranibizumab) J2778
Nufymco® (ranibizumab-leyk) J3590
Ranibizumab-nuna Q5124
Susvimo™ (ranibizumab) J2779

Background Information:

- Intravitreal injections of anti-vascular endothelial growth factor (VEGF) have been widely used by ophthalmologists to treat a variety of ocular diseases. They are injected directly into the eye to prevent the formation of new blood vessels and reduce blood vessel leakage and inflammation. The following anti-VEGF therapies are currently available to treat the following indications:

    - Byooviz: macular edema due to retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), and neovascular (wet) age-related macular degeneration (AMD)

    - Cimerli: diabetic macular edema (DME), diabetic retinopathy (DR), macular edema due to RVO, mCNV, and wet AMD

    - Lucentis: DME, DR, macular edema due to RVO, mCNV, and wet AMD

    - Nufymco: DME, DR, macular edema due to RVO, mCNV, and wet AMD

    - Susvimo: neovascular AMD and DME in those who have previously responded to at least two intravitreal injections of a VEGF inhibitor

- Age-related Macular Degeneration

    - Age-related macular degeneration is a degenerative disease of the macula that results primarily in loss of central vision. Wet AMD is characterized by growth of abnormal vessels into the subretinal space. These abnormal blood vessels leak leading to collections of subretinal fluid and/or blood beneath the retina. The 2022 American Academy of Ophthalmologists (AAO) Age-Related Macular Degeneration Preferred Practice Pattern Guidelines recommend observation and early detection, antioxidant vitamin and mineral supplements, and intravitreal injections of anti-VEGF agents for the management of wet AMD. Guidelines recommend Eylea™, Avastin®, Vabysmo™, or Lucentis for treatment. The guidelines have not been updated with Beovu®, Byooviz, and Susvimo.

- Diabetic Retinopathy and Diabetic Macular Edema

    - Diabetic retinopathy and DME are common complications and the ocular manifestations of end-organ damage in diabetes mellitus. The 2025 AAO Diabetic Retinopathy Preferred Practice Pattern Guidelines state the goals of therapy for DR and DME include improvement or stabilization of visual function, improvement in vision-related quality of life, and optimal control of blood glucose, blood pressure, and other metabolic risk factors. Patients should always be treated with anti-VEGF therapy if they have severe non-proliferative DR or proliferative DR with center-involved macular edema. In cases of mild to moderate non-proliferative DR with center-involved macular edema, patients should also receive intravitreal injections. The guidelines support the use of Lucentis, Eylea, Vabysmo, and Avastin. AAO recommendations were based on trials comparing Eylea, Avastin, and Lucentis to focal laser treatment. All trials showed that treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years compared to laser treatment.

- Retinal Vein Occlusion

    - Retinal vein occlusion occurs when there is partial or complete obstruction of a retinal vein. Vision loss can occur with RVO and is associated with macular ischemia or edema, retinal hemorrhages, vitreous hemorrhage, or epiretinal membrane formation. The 2025 AAO Retinal Vein Occlusions Preferred Practice Pattern Guidelines recommend anti-VEGF therapy as first-line treatment for macular edema caused by RVO. The guidelines support the use of Lucentis, Eylea, and Avastin. The guidelines state VEGF inhibitors, Eylea, Avastin, and Lucentis, are more effective than sham injection or laser therapy in maintaining or improving visual acuity in patients with macular edema secondary to RVO.

- Myopic Choroidal Neovascularization

    - Myopic choroidal neovascularization is a common vision-threatening complication of myopia and pathological myopia. Naïve myopic patients who present with blurred vision, vision loss, or metamorphopsia should be referred to a retinal specialist who can diagnose mCNV. Once mCNV is diagnosed, anti-VEGF therapy should be started immediately. Lucentis has demonstrated improvements in visual acuity in patients with mCNV. A randomized controlled trial compared the effects of Lucentis to photodynamic therapy with verteporfin in patients with mCNV. At month three, treatment with Lucentis demonstrated significant improvements in visual acuity compared to photodynamic therapy with verteporfin. A Cochrane systematic review concluded that there is low to moderate-certainty evidence for the efficacy of VEGF inhibitors to treat mCNV at one year and two years. It also concluded that Lucentis and Avastin are equivalent in terms of efficacy in the treatment of patients with mCNV.

- There are very few randomized control trials that assess the efficacy of one anti-VEGF therapy over another. Of the two that are available, Avastin, Eylea, and Lucentis were all shown to be non-inferior to each other, and because of this, choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability. However, a 2015 study conducted by Wells, et al. did show Eylea was superior to Avastin therapy when patients had a visual acuity of less than or equal to 20/50. In addition, a subcohort analysis of the YOSEMITE AND RHINE trials showed Vabysmo demonstrated BCVA gains similar to aflibercept, while demonstrating numerically greater improvements in anatomic outcomes at years 1 and 2. Therefore, in these scenarios Avastin should not be used prior to Eylea or Vabysmo.

- Susvimo

    - In the ARCHWAY clinical trial, Susvimo was only implanted following at least 3 prior anti-VEGF intravitreal injections of either Avastin, Eylea, or Lucentis within 6 months of screening. Patients in the study had to demonstrate anatomic and visual response to anti-VEGF treatment for nAMD, therefore, Susvimo should not be administered to patients who have not had proven success with prior anti-VEGF therapy.

    - Susvimo was not studied with supplemental doses of other anti-VEGF therapies and therefore, should not be administered with any other intravitreal injections other than Lucentis. Supplemental doses were given when the study participants experienced one of the following: decrease of 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or more from the best-recorded BCVA in the study; an increase of 150 µm or more in retinal thickness measured by central subfield thickness (CST) on spectral domain OCT (SD-OCT) from the lowest CST measurement in the study; or an increase of 100 µm or more in CST on SD-OCT from the lowest CST measurement in the study associated with a decrease of 10 ETDRS letters or more from the best-recorded BCVA during the study. In these scenarios only should patients be considered for additional Lucentis injections. Fifteen ETDRS letters are equivalent to a decrease in visual acuity by half.

    - Of the 1.6% of patients who required supplemental injections with Lucentis during the study, a maximum of 2 injections were given per affected eye within the 24 weeks between implantation of the device of the first refill. As such, there is no data available to support more than 2 supplemental injections per 6 months.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 02/12/2026	Updated to include Nufymco
1.5	Effective Date: 12/04/2025	Updated to include ranibizumab-nuna
1.4	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/08/2023	Updated to add criteria stating the biosimilars will be covered for all FDA approved indications of the innovator product and add a step through Byooviz

1.1	Effective Date: 04/06/2023	New policy. This policy replaces previously approved criteria that was embedded in the Intravitreal Injections for Retinal Conditions Policy which is being split into individual drug policies and retired. The authorization period was updated from up to 1 year to at least 60 days and up to 1 year
1.0	Effective Date: 01/01/2021	New Policy

Reblozyl® (luspatercept-aamt)
HCPCS: J0896

Background Information:

- Beta-thalassemia

- The term "thalassemia" refers to a group of blood disorders characterized by a decrease or absence of synthesis of normal hemoglobin globulin chains. According to the chain whose synthesis is impaired, the thalassemias are call α-, β-, γ-, δ-, δβ-, or εγδβ-thalassemias. Beta-thalassemias result from a genetic defect in the HBB gene leading to a reduction in production of β-globulin chains, an excess of α-globulin chains, and a decrease in functioning hemoglobin. Low levels of hemoglobin cause a lack of oxygen in many parts of the body and anemia. People with anemia in beta-thalassemia often require lifelong blood transfusions for survival and subsequent treatment for iron overload due to these transfusions.

- The 2021 International Thalassemia Federation guidelines for transfusion dependent thalassemias recommend diagnosis should begin with genetic testing because of the extreme diversity in clinical severity of thalassemia subtypes. The degree of excess nonfunctional α-chains is the major predictor of disease severity. The less β-globulin production, the more non-functional α-chains in the bloodstream. β_0-thalassemia refers to the complete absence of production of β-globulin. When patients are homozygous for a β_0-thalassemia gene, they cannot make any normal β-chains. β_+-thalassemia indicates a mutation that presents decreased but not absent production of β-globulin. In thalassemia patients in which one or both of their β-thalassemia mutations are β_+-mutations, the disorder may be less severe. Beta-thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta-thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype. Reblozyl was not studied in patients with S/β-thalassemia or α-thalassemia. Patients with other β-thalassemia subtypes that were transfusion dependent were included in the clinical trial.

- Treatment guidelines also recommend all patients undergo at least an annual comprehensive assessment at a thalassemia center. During such an assessment, recommendations are summarized after consultation with multiple specialists including a hematologist, a nurse specialist, a hepatologist, a cardiologist, an endocrinologist, a psychologist, a genetics counselor, a social worker, and a dietitian.

- Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. Continuation of infusions can be assessed by withholding transfusions and monitoring weekly hemoglobin levels. If the hemoglobin drops under 7 g/dL on two occasions two weeks apart, then regular transfusions should be commenced. Guidelines define a

patient as transfusion dependent when they are getting infusions of packed red blood cells every 2 – 5 weeks to maintain the pre-transfusion hemoglobin of 9 g/dL - 10.5 g/dL and the post-transfusion hemoglobin less than 14 - 15 g/dL. This translates to approximately 100 mL/kg/year of packed red blood cells.

- Guidelines recommend the use of Reblozyl in patients who are regularly transfused and have a hemoglobin of less than 11 g/dL when not influenced by a recent red blood cell transfusion. They also state that if improvement is not seen following the first 3 doses, or after 9 weeks of therapy, Reblozyl should be discontinued.

- Myelodysplastic Syndrome

- Myelodysplastic syndromes are a group of blood cancers that occur as a result of disordered development of blood cells within the bone marrow. The World Health Organization has classified six types of MDS based on how many early cell types show dysplasia, the type of cytopenias a patient is experiencing, the portion of ring sideroblasts, the portion of blasts in the blood or bone marrow, and the type of genetic mutations in the bone marrow cells. In ESA treatment experienced patients, Reblozyl was only studied in patients with the MDS with ring sideroblasts (MDS-RS) subtype. In this subtype, patients have ring sideroblasts greater than or equal to 15% of erythroid precursors in bone marrow or greater than or equal to 5% if the SF3B1 mutation is present. They also present with less than 5% blasts in the bone marrow. Patients with the MDS-RS subtype do not have MDS associated with a del 5q cytogenetic abnormality. The classification system for MDS automatically classifies patients with the del 5q mutation as a separate unique subtype. This subtype was also not included in the clinical trial assessing efficacy of Reblozyl in ESA treatment naïve patients.

- One in three patients with MDS will progress to acute myeloid leukemia (AML). Risk of disease progression to AML and risk of mortality are assessed using the Revised International Prognostic Scoring System (IPSS-R). The IPSS-R categorizes patients into 1 of 5 groups, from very low risk to very high risk using the patient's disease presentation including cytogenic groups, percentage of medullary blasts, hemoglobin, platelets, and absolute neutrophil count. The IPSS-R can help determine whether to treat or observe patients at the time of diagnosis. Reblozyl was only studied in patients classified as very low, low, or intermediate risk using the IPSS-R in all clinical trials.

- Reblozyl for use in ESA treatment experienced patients was approved based on the results of the MEDALIST trial, a phase III, placebo-controlled study in 229 patients with very low, low, or intermediate risk non-del(5q) MDS with ring sideroblasts. All patients were red blood cell transfusion-dependent defined as anemia requiring at least 2 units of red blood cells over 8 weeks. Patients had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents (ESAs) or were intolerant to ESA therapy. Refractory was defined as non-response or response that is no longer maintained to prior ESA therapy of either recombinant human erythropoietin at a dose of 40,000 IU/week for at least 8 weeks or darbepoetin alpha greater than 500 µg every 3 weeks for at least 4 doses. Patients were considered unlikely to respond when they had an endogenous serum erythropoietin level greater than 200 U/L. Patients must not have used any prior therapy with disease-modifying agents for underlying MDS disease and must not have secondary MDS known to have arisen as the result of chemical injury or

treatment with chemotherapy or radiation for other diseases. The primary endpoint was transfusion independence for 8 weeks or longer during weeks 1 through 24. The primary endpoint was observed in 38% of the patients in the Reblozyl group compared with 13% of those in the placebo group (p-value < 0.001).

- Reblozyl for use in ESA treatment naïve patients was approved based on the results of the COMMANDS trial, a phase III, open-label, randomized controlled study of 356 patients with myelodysplastic syndromes of very low risk, low risk, or intermediate risk. Subjects had not experienced prior treatment with ESAs and required regular red blood cell transfusions of at least 2 – 6 packed red blood cell units per 8 weeks for greater than or equal to 8 weeks immediately before randomization. Patients must not have MDS associated with del 5q cytogenetic abnormality or secondary MDS known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases. The primary endpoint was red blood cell transfusion independence for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL during weeks 1 – 24. Results showed 58.5% of patients treated with Reblozyl vs. 31.2% of patients treated with epoetin alfa achieved the primary endpoint (p-value < 0.0001).

- The current NCCN guidelines recommend ESA treatment in all patients unless their serum epopoietin is greater than 500 mU/mL or those with IPSS-R very low, low, or intermediate disease without a del(5q) mutation with RS greater than or equal to 15% or RS greater than or equal to 5% with an SF3B1 mutation. In instances where a patient presents with an eoppoietin greater than 500 mU/mL or IPSS-R very low, low, or intermediate disease without a del(5q) mutation with RS greater than or equal to 15% or RS greater than or equal to 5% with an SF3B1 mutation, guidelines recommend Reblozyl as first-line therapy.

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Policy History		
#	Date	Change Description
1.8	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.7	Effective Date: 10/03/2024	Updated authorization period to state “aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days and up to 6 months at a time” and added an exception to ESA use in those with IPSS-R very low, low, or intermediate disease without a del(5q) mutation with ring sideroblasts (RS) greater than or equal to 15% or RS greater than or equal to 5% with an SF3B1 mutation
1.6	Effective Date: 10/12/2023	Updated to remove prescriber requirements, the sideroblast requirements in myelodysplastic syndrome, and require ESA’s as first-line therapy unless a patient has serum epopoietin greater than 500 mU/mL.
1.5	Effective Date: 06/08/2023	Updated to remove the statement not allowing use with other disease modifying therapies
1.4	Effective Date: 12/01/2022	Updated to include the trial and failure of preferred products statement
1.3	Effective Date: 10/06/2022	Update to remove statement not allowing use with gene therapy

1.2	Effective Date: 08/04/2022	Annual review of medical policy. No changes to the criteria were made at this time
1.1	Effective Date: 08/12/2021	Updated to remove the upper limit on ring sideroblast when the SF3B1 mutation is present
1.0	Effective Date: 11/01/2021	New Policy

Rebyota® (fecal microbiota, live-jslm)
HCPCS: J1440

Background Information:

- Rebyota is indicated for the prevention of recurrence of CDI in individuals 18 years of age and older following antibiotic treatment for recurrent CDI.

    - In the pivotal Phase III PUNCH CD3 trial, which was utilized for FDA approval of this therapy, inclusion criteria included documentation of recurrent CDI (defined as one or more recurrences after a primary episode) in participants who had completed one or more rounds of standard-of-care antibiotic therapy OR had two or more episodes of severe CDI resulting in hospitalization in the last year, a positive stool test within 30 days of enrollment, and participants must have been taking or have just been prescribed antibiotics to control recurrent CDI symptoms. There was a 24-72 hour antibiotic washout period prior to Rebyota therapy. These specific inclusion criteria are included in the policy due to the narrow treatment window that Rebyota offers.

        - Patients were treated with a single 150 mL rectal dose. The primary endpoint was treatment success, defined as the absence of CDI diarrhea within 8 weeks of study treatment. The estimated rate of treatment success was 70.6% in the Rebyota group (95% Credible Interval, 64.1%-76.8%) compared to placebo 57.5% (95% Credible Interval, 48.1%-67.1%). In this trial, patients who did not experience treatment success at week 8 were given a 2nd dose. Determining treatment failure can take up to 8 weeks, and an authorization period of 2 months would allow for a one-time repeat dose of Rebyota after the initial authorization period. Data that supports continued Rebyota treatment does not exist. Currently, data only supports one repeat course of treatment.

    - The 2021 IDSA/SHEA Guideline Update recommends use of adjunctive therapy for prophylaxis after one recurrent CDI episode treated with appropriate antibiotics.

        - These guidelines recommend the use of Rebyota alternative, Zinplava, for patients with recurrent CDI episode within the last 6 months, as an adjunctive treatment to antibiotics (fidaxomicin, vancomycin, etc.) rather than antibiotics alone. Zinplava is an IV administered monoclonal antibody that is given as a single infusion over 60 minutes. Zinplava is FDA approved to reduce the recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.

        - The guidelines state the balance of benefits and harms favor adding Zinplava to SOC antibiotics for patients with a CDI episode and at least 1 risk factor for recurrence (recurrent CDI episode within the last 6 months, age ≥ 65 years, immunocompromised host, and severe CDI on presentation), however treatment seems more favorable in patients with multiple risk factors of

recurrent CDI and especially in patients with a prior CDI in the last 6 months. Current guidelines do not favor the use of Zinplava or FMT over the other for prevention of recurrence of CDI. Zinplava was the only FDA approved option for prevention of recurrence of CDI when the 2021 IDSA/SHEA guidelines were published.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 02/12/2026	Annual review- no changes to the criteria were made
1.3	Effective Date: 03/31/2025 P&T Date: 02/13/2025	Updated criteria to include not to be used in combination with Zinplava or Vowst.
1.2	Effective Date: 02/08/2024	Annual review – no changes to the criteria were made.
1.0	Effective Date: 05/01/2023	New policy

Rituximab Class Policy
Riabni™ (rituximab-arrx) Q5123
Rituxan® (rituximab) J9310; J9312
Rituxan Hycela® (rituximab and hyaluronidase human) J9311
Ruxience™ (rituximab-pvvr) Q5119
Truxima™ (rituximab-abbs) Q5115

Background Information:

- Rituxan Hycela is a combination of rituximab and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with:
    - Follicular lymphoma (FL)
        - Relapsed or refractory follicular lymphoma as a single agent
        - 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
        - Non-progressing follicular lymphoma as a single agent after first-line CVP chemotherapy
    - Previously untreated diffuse large B-cell lymphoma (DLBCL) in combination with CHOP or other anthracycline-based chemotherapy regimens
    - Previously untreated and previously treated CLL in combination with FC
    - Limitations of use:
        - Treatment should only be initiated 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

- Rituxan Hycela is a combination of rituximab and hyaluronidase, an enzyme that helps deliver rituximab under the skin, and can be given subcutaneously versus intravenously as with Rituxan. Rituxan Hycela cannot be given before a patient has received at least one full dose of intravenous Rituxan without adverse effects and, because of this, there would be no clinical necessity for a patient to switch from Rituxan to Rituxan Hycela as it offers no clinical safety or efficacy advantages over the intravenous product.

- NCCN guidelines state an FDA approved biosimilar can be substituted for Rituxan. The guidelines do not specify what biosimilars are appropriate for a specific tumor type which allows for use of any of the biosimilars to be used for any indication the innovator product is FDA approved for.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 06/05/2025	Updated to remove the statement requiring a rationale for use of Rituxan Hycela over rituximab and added a statement requiring trial and failure of intravenous rituximab prior to use of Rtiuxan Hycela
1.2	Effective Date: 04/10/2025	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 01/01/2024	New Policy

Rivfloza™ (nedosiran)
HCPCS: J3490

Background Information:

- Rivfloza is a small interfering ribonucleic acid (siRNA) that inhibits the production of the hepatic lactase dehydrogenase (LDH) enzyme – an enzyme that is involved in the conversion of glyoxylate to oxalate. Rivfloza is approved to lower urinary oxalate levels in children 2 years of age and older and adults with PH1 and relatively preserved kidney function, e.g., eGFR ≥ 30 ml/min/1.73 m^2.

- Primary hyperoxaluria (PH) is an ultra-rare genetic disease characterized by recurrent kidney and bladder stones. There are three types of PH that differ in their severity and underlying genetic mutation: PH1, PH2, and PH3. PH1 is the most common form of PH, accounting for around 80% of total cases and affecting approximately 3,000 to 5,000 patients in the US. PH1 patients have a mutation of the AGXT gene, which results in decreased or absent hepatic enzyme alanine-glyoxylate aminotransferase (AGT). AGT converts glyoxylate to glycine, and a decrease or absence of AGT brings about an increase in glyoxylate and oxalate. The excess production of oxalate by the liver results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones, nephrocalcinosis, progression to kidney failure, and systemic organ dysfunction. PH1 can be suspected in patients with increased urinary oxalate excretion, indicated by levels >1 mmol/1.73 m^2 per day. Genetic testing for a mutation in the AGXT gene confirms the PH1 diagnosis.

- Conservative treatment is generally recommended following a diagnosis of PH1, which includes hyperhydration, alkalizing the urine, and trialing pyridoxine. Hyperhydration is a common supportive measure for management of PH1. Increasing fluid intake to 3 L/m^2 body surface area (BSA) per day can create higher urinary output, which decreases tubular fluid oxalate concentration and intratubular deposition, thereby preventing oxalate accumulation in the kidney. Experts recommend this approach of increasing fluid intake to help manage PH1. Pediatric patients may require a gastronomy tube to meet the high daily fluid requirement. Urinary alkalinization should also be started to prevent stone formation. Potassium citrate (0.1 to 0.15 g/kg) can be used to decrease the amount of calcium oxalate. The citrate component will allow calcium citrate to form, which is much more soluble than calcium oxalate. Urinary pH must be kept between 6.2 and 6.8 to be alkaline.

- Prior to the approval of Oxlumo and Rivfloza, high-dose vitamin B-6 (pyridoxine), a cofactor for the AGT enzyme, was the only treatment proven to target the underlying pathophysiology of PH1. In 30-50% of PH1 patients, vitamin B-6 reduces oxalate levels and prevents accumulation in the kidneys. Responsiveness to vitamin B-6 is defined as a >30% decrease in urinary oxalate excretion after a minimum trial period of 3-6 months at the maximum tolerated dose. Experts recommend a starting dose of 5 mg/kg/day, with a maximum daily dose of 20 mg/kg. Sensory neurotoxicity is a rare, dose limiting side effect of vitamin B-6.

- Oxlumo was the first FDA-approved medication indicated for the treatment of PH1 to lower urinary and plasma oxalate levels in pediatric and adult patients. Oxlumo is an RNA interference therapy that reduces levels of the glycolate oxidase (GO) enzyme by targeting mRNA in the hepatocytes. Decreased GO enzyme levels reduce the amount of available glyoxylate, which is the substrate for oxolate production. The GO enzyme is upstream from the deficient AGT enzyme that causes PH1; therefore, the mechanism of action of Oxlumo is independent of the underlying AGXT gene mutation.

- The safety and efficacy of Rivfloza was established in the randomized, double-blind, placebo-controlled Phase II PHYOX2 trial which enrolled 35 patients aged 6 years or older with PH1 or PH2 and an eGFR ≥ 30 ml/min/1.73 m^2. Too few patients were enrolled to evaluate the efficacy in the PH2 population, therefore Rivfloza is only indicated for patients with PH1. Key exclusion criteria included prior kidney or liver transplantation, current or planned dialysis during the trial period, planed transplantation during the trial period, and use of an RNAi drug within the last 6 months.

    - Patients were randomized to receive monthly doses of Rivfloza (n=23) or placebo (n=12). The Rivfloza dose for patients at least 12 years of age weighing at least 50 kg was 160 mg, for patients at least 12 years of age weighing less than 50 kg was 128 mg, and for children 6 to 11 years of age was 3.3 mg/kg (to a maximum of 128 mg).

    - The primary endpoint was the area under the curve, from days 90 to 180, of the percent change in baseline in 24-hour urinary oxalate excretion (AUC24-hour Uox). The least-squares (LS) mean AUC24-hour Uox was -3486 in the Rivfloza group compared to +1490 in the placebo group, for a between group difference of 4976.

    - The LS mean percent change from baseline in 24-hour urinary oxalate excretion averaged over days 90, 120, 150, and 180 was -37% in the Rivfloza group and 12% in the placebo group for a between group difference of 49%. Among patients with PH1, the between group difference was 56%.

- Clinical trials have shown that Oxlumo and Rivfloza can effectively treat the underlying pathophysiology of oxalate overproduction. Data to show that Oxlumo or Rivfloza delays or precludes the need for liver and/or kidney transplantation will impact these therapies prospective value.

    - Systemic oxalosis is defined as the spread of oxalate to organs outside of the kidneys, such as the joints, skin, bones, and heart. This can lead to organ dysfunction and death. One registry study found that around 40% of patients present with end-stage renal disease (ESRD) at the time of PH1 diagnosis, representing a significant proportion of the PH1 patient population.

    - In patients with PH1, aggressive hemodialysis is indicated once plasma oxalate levels exceed 30 mmol/L to prevent systemic oxalosis. Patients with PH1 and advanced renal disease carry a higher risk for systemic oxalosis, as renal excretion of oxalate is greatly reduced as eGFR declines, leading to an increase in plasma oxalate levels. Peritoneal dialysis alone does not achieve sufficient oxalate clearance; however, peritoneal dialysis in combination with hemodialysis may be necessary for those who do not respond to hemodialysis alone.

    - Dialysis is often used as a bridge to future liver and/or kidney transplantation in patients with PH1. Patients with a history of liver and/or kidney transplantation were excluded from all Oxlumo and Rivfloza trials, as removal of the patient's native liver is considered curative by removing the source of oxalate overproduction. Subsequent kidney transplantation or simultaneous liver-kidney transplantation may be required for those with ESRD. The role of transplantation in the setting of PH1 may change in the future with the introduction of small-interfering RNA therapies. However, additional long-term data is needed to understand whether these therapies can delay or eliminate the need for liver and/or kidney transplantation in patients with PH1.

- In 2023, OxalEurope and European Rare Kidney Disease Reference Network (ERKNet) released clinical practice recommendations for primary hyperoxaluria: an expert consensus statement. The highlights of these recommendations include:

    - Recommendation of generic testing of each patient with high clinical and/or biochemical suspicion of PH (A: strong recommendation).

    - Conservative treatment is recommended promptly in all patients with suspected PH (B: strong recommendation). Conservative treatment includes starting hyperhydration (3.5-4 l/day in adults, 2-3 l/m2 BSA in children, to be consumed throughout 24 hours) in all patients with suspected PH and preserved kidney function (A-B: strong recommendation). They recommend oral administration of potassium citrate (0.1–0.15 g/kg) in patients with preserved kidney function (C – moderate recommendation). In addition, they recommend testing pyridoxine responsiveness in all patients with PH1 and titrating its dose based on urinary oxalate excretion (A: strong recommendation). They also recommend that all patients with PH1 are tested for pyridoxine responsiveness; urine oxalate measurements should be repeated on at least two occasions after at least 2 weeks of pyridoxine administration for evaluation of pyridoxine responsiveness, defined as a mean decrease of >30% between the two samples.

    - RNAi therapy is recommended under a multitude of conditions including:

        - PH1 is genetically established AND

        - Pyridoxine unresponsiveness or partial responsiveness is biochemically established OR have a mutation consistent with pyridoxine unresponsiveness

        - Urine oxalate excretion is > 1.5 times the upper reference limit AND

        - Patients demonstrate a clinical phenotype of PH1, characterized by active stone disease AND/OR nephrocalcinosis AND/OR renal impairment (B: moderate recommendation) OR patients have no ongoing clinical disease (C: weak recommendation).

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Policy History		
#	Date	Change Description
1.2	Effective Date: 12/04/2025	Annual review completed, no changes to criteria. Added ERKNet/OxalEurope clinical practice recommendations.
1.1	Effective Date: 12/12/2024	Annual review of policy
1.0	Effective Date: 02/12/2024	New policy

Roctavian™ (valoctocogene roxaparvovec)
HCPCS: J1412

Background Information:

- Roctavian is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A without antibodies to adeno-associated virus serotype 5 (AAV5).

- Hemophilia A is a rare genetic bleeding disorder in which affected individuals have insufficient levels of factor VIII. It is the second most common type of hemophilia and caused by mutations in the F8 gene. The F8 gene is located on the X chromosome and thus the disease is inherited as an X-linked recessive trait. About 30% of cases are the result of spontaneous genetic mutations. Overall incidence is estimated at 1 in 5,000 male births.

- The symptoms and severity of hemophilia A may vary greatly from one person to another. Hemophilia A can range from mild to moderate to severe.

- Mild hemophilia patients have a factor activity of 5% to 40% and usually do not experience any major problems in everyday life. It often goes unnoticed until puberty or adulthood when bleeding after surgery or a deep cut lasts longer than normal. These patients do not typically need prophylactic therapy and only require on-demand factor for injuries or surgeries.

- Moderate hemophilia patients have a factor activity of 1% to 5% and may have occasional episodes of spontaneous bleeding from deep tissues such as joints and muscles. These episodes are usually associated with some injury or inciting event. Individuals with moderate hemophilia A are at risk for prolonged bleeding following surgery or trauma. Affected individuals are usually diagnosed by 5 or 6 years of age. The frequency of spontaneous bleeding episodes in individuals with moderate hemophilia A is highly variable resulting in some patients needing consistent prophylactic factor VIII and others only needing on-demand factor VIII for medical procedures.

- Severe hemophilia patients have a factor level of less than 1% and often have bleeding for no known reason, especially in the joints and muscles. From infancy, patients bruise easily and as they become more active, learn to walk, and put more strain on their joints and muscles, bleeding starts to occur. Without preventative treatment, a young child may experience 2 to 5 spontaneous bleeding episodes per month.

- Hemophilia A should be suspected in individuals presenting with a history of easy bruising, spontaneous bleeding, particularly into the joints, muscles, and soft tissues, or excessive bleeding following trauma or surgery. If hemophilia is suspected, the clinician should obtain the patient's bleeding history and family history of abnormal or unexplained bleeding experienced by any siblings or maternal male relatives to assess patterns of inheritance and assist with diagnosis. A definitive hemophilia A diagnosis is based on a factor assay to demonstrate a

deficiency of factor VIII. Once an individual is diagnosed with hemophilia A, the specific mutation in the F8 gene responsible for causing hemophilia may be identified.

- The current standard of care for hemophilia A is the use of factor VIII replacement therapy. There are two types of factor products available to treat hemophilia which include plasma derived factor, entirely made of plasma from human donations and recombinant factor, which is made by genetically engineered technology, both with standard and extended half-life products. All factor products have demonstrated to have similar safety and efficacy in clinical studies treating or reducing bleeding episodes with the apparent difference in the frequency of administration: up to three times weekly injections for standard products and weekly or every two weeks for extended half-life products. To be enrolled in the GENEr8-1 trial, patients needed to be stable on factor VIII therapy for 12 months prior Roctavian administration.

- Hemlibra (emicizumab) is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX and factor X to restore the function of missing activated factor VIII in hemophilia A patients to restore hemostasis. It can be used to treat patients without inhibitors who continue having spontaneous bleeds on prophylactic factor VIII therapy. Failure of Hemlibra is denoted by spontaneous soft tissue bleeds, micro-bleeding into a joint, or ongoing joint pain of a known target joint.

- It is estimated that up to 30% of individuals with severe hemophilia A develop inhibitors against factor VIII replacement therapy. Inhibitors most often develop during childhood, especially during the first 20 exposure days. Exposure days are counted as a day during which a patient receives factor. Controlling bleeds is a greater challenge in hemophilia patients with inhibitors than in those without. Inhibitors to factor VIII are associated with a higher disease burden, including increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges, all of which may impact a patient's physical functioning, capacity for physical activities, and quality of life. The definition of a positive inhibitor is a Bethesda titer of greater than or equal to 0.6 BU for factor VIII. Patients positive for factor VIII inhibitors or with a prior history of factor VIII inhibitors were excluded from the GENEr8-1 trial. In order to limit the risk of inhibitor development following Roctavian therapy, the GENEr8-1 study also required patients had greater than 150 prior exposure days to factor IX therapy before receiving gene therapy.

- Roctavian uses an AAV5 vector to deliver a functional copy of the F8 gene to the patient's liver where functional factor VIII is produced. Patients with high AAV5 antibody titers may not respond to gene therapy due to the antibodies neutralizing Roctavian before the functional F8 gene can be properly incorporated into the patient's genome. The GENEr8-1 study excluded patients from the trial based on antibody titers and is only indicated in those without AAV5 antibodies.

- Roctavian has not been studied and there is no data to support use in combination with other gene therapies indicated for use in hemophilia A.

- A provider portal is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

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Policy History		
#	Date	Change Description
1.3	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 08/10/2023	New policy. This criteria replaces previously approved preliminary criteria
1.0	Effective Date: 07/18/2023	New Policy

Ryoncil® (remestemcel-L)
HCPCS: J3402

Background Information:

- Ryoncil is an allogeneic bone marrow-derived mesenchymal stromal cell (MSC) therapy indicated for the treatment of steroid-refractory acute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older.

- Acute GVHD occurs in approximately 50% of patients who receive an allogeneic bone marrow transplant (BMT). Over 30,000 patients worldwide undergo an allogeneic BMT annually, primarily during treatment for blood cancers, including about 20% in pediatric patients. SR-aGVHD is associated with mortality as high as 90% and significant extended hospital stay costs. Prior to the approval of Ryoncil, there were no FDA-approved treatments in the US for children under 12 with SR-aGVHD. GVHD has been classically divided into acute and chronic variants based on the time of onset using a cutoff of 100 days. However, this conventional division has been challenged by the recognition that signs of acute and chronic GVHD may occur outside of these designated periods. Acute GVHD manifestations include: classic maculopapular rash, abdominal cramps with diarrhea, and rising serum bilirubin concentration. Patients who demonstrate progression of disease by day 5 or nonresponse by day 7 are considered to have corticosteroid resistance.

- The National Comprehensive Cancer Network (NCCN) Hematopoietic Cell Transplantation (HCT) guidelines Version 1.2023 recommend Jakafi as a category 1 option for patients with SR-aGVHD. At this time, Jakafi is only indicated for patients 12 years and older with SR-aGVHD. Per UpToDate for patients with aGVHD grade 2 or higher, systemic glucocorticoids are recommended.

- The safety and effectiveness of Ryoncil were evaluated in a multicenter, single-arm study in 54 pediatric study participants with SR-aGVHD after undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). The study enrolled pediatric patients with SR-aGVHD Grade B to D (excluding Grade B skin alone) as per International Blood and Marrow Transplantation Registry Severity Index Criteria (IBMTR) after receiving allo-HSCT. SR-aGVHD was defined as aGVHD that progressed within 3 days or did not improve within 7 consecutive days of treatment with methylprednisolone 2 mg/kg/day or equivalent.

- The main efficacy outcome measures were Day-28 overall response rate (complete response rate and partial response rate) and the duration of response.

- The overall response rate was 70% with sixteen study participants (30%) having had a complete response to treatment 28 days after receiving Ryoncil, and 22 study participants (41%) having had a partial response.

- Overall response rate at Day-28 by baseline disease severity is as follows: Grade B (3/6; 50%), Grade C (16/23; 70%), and Grade D (19/25; 76%).

- The median duration of response, as calculated from Day-28 response to either progression (worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment), new systemic therapy for aGVHD, or death from any cause, was 54 days.

References:

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Policy History		
#	Date	Change Description
1.1	Effective Date: 02/12/2026	Annual review – No changes to the criteria were made at this time
1.0	Effective Date: 03/03/2025	New Policy

Rystiggo® (rozanolixizumab-noli)
HCPCS: J9333

Background Information:

- Rystiggo is a neonatal Fc receptor blocker indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or antimuscle-specific tyrosine kinase (MuSK) antibody positive

- Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, MuSK, and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular, or class I, MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Depending on the severity of muscle weakness, at this point MG is classified as either class II for mild, class III for moderate, and class IV for severe presentation. Those with class V disease require intubation due to profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Rystiggo has only been studied in patients with class II – IV disease. There is no safety and efficacy data to support use in patients with class I or V disease at this time.

- Rystiggo is only indicated for use in patients with anti-AChR or anti-MuSK antibodies. An immunologic assay to detect for the presence of anti-AChR and anti-MuSK antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has one of these antibody types, at least one other confirmatory test should be conducted. A positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) all can be used to verify anti-AChR MG. Only a repetitive nerve stimulation (RNS) or single-fiber electromyography (SFEMG) can be used to confirm anti-MuSK antibody positive disease.

- The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. MuSK antibody positive disease is not typically associated with thymic abnormalities or thymoma. The 2021 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery. Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Rystiggo has not been studied in patients who have undergone thymectomy within 6 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Rystiggo in these patient populations at this time regardless of antibody status.

- Safety and efficacy of Rystiggo were established in the MycarinG trial, a multicenter, randomized, double-blind, placebo-controlled study of 200 adult patients with gMG who were anti-AChR antibody positive or anti-MuSK antibody positive. Patients had class II – IV disease and were already stable on at least one treatment, which included acetylcholinesterase inhibitors, corticosteroids, or immunosuppressants, for MG prior to study entry. They also had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 3 with at least 3 points from non-ocular symptoms. Patients were randomly assigned 1:1:1 to receive weight-tiered doses of Rystiggo equivalent to approximately 7 mg/kg or approximately 10 mg/kg or placebo administered as six subcutaneous infusions per cycle with one infusion given per week repeated as needed depending on clinical response no sooner than 63 days after initiation of the previous cycle. The primary endpoint the change from baseline to day 43 in the myasthenia gravis activities of daily living (MG-ADL) score. The trial met its primary endpoint with reductions in MG-ADL score from baseline to day 43 were greater in the Rystiggo 7 mg/kg group and in the Rystiggo 10 mg/kg group than with placebo which was statistically significant for both groups (p-value < 0·0001).

- Standard therapies recommended by the 2021 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, rituximab, Soliris®, IVIG, and PLEX.

- Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.

- Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect doses should be maintained for six months to two years of therapy and then tapered to the lowest effective dose.

- Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents that are better supported by randomized clinical trial data.

- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.

- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX. Patients were excluded from the ADAPT trial if they had received IVIG or undergone PLEX 1 month prior to the start of the study.

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. Treatment guidelines state rituximab should be considered as an early therapeutic option in patients with MuSK antibody positive MG who have an unsatisfactory response to initial immunotherapy. The efficacy of rituximab in refractory AChR antibody positives MG is uncertain. It is an option if patients fail or do not tolerate other immunosuppressive agents. Patients were excluded from the ADAPT trial is they had used rituximab 6 months prior to the start of Vyvgart therapy.

- Soliris should be considered in the treatment of severe, refractory, AChR antibody positive generalized MG. Until further data become available to allow comparisons of cost and efficacy with other treatments guidelines state, Soliris should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals. Pateints were excluded from the ADAPT trial is they had received Soliris 6 months prior to the start of Vyvgart therapy.

- Rystiggo have not been studied and there is no data to support use in combination with other medications used to treat MG, such as, Soliris.

References:

1. Rystiggo [prescribing information. Smyrna, GA: UCB, Inc.; March 2025.
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Policy History		
#	Date	Change Description
1.3	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 08/10/2023	New Policy
1.0	Effective Date: 07/18/2023	New Policy

Rytelo™ (imetelstat)
HCPCS: J0870

Background Information:

- Rytelo is an oligonucleotide telomerase inhibitor indicated for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell (RBC) units over 8 weeks who have not responded to, have lost response to, or are ineligible for erythropoiesis-stimulating agents (ESA).

- MDS are a group of blood cancers that occur as a result of disordered development of blood cells within the bone marrow. The World Health Organization (WHO) has classified six types of MDS based on how many early cell types show dysplasia, the type of cytopenias a patient is experiencing, the portion of ring sideroblasts, the portion of blasts in the blood or bone marrow, and the type of genetic mutations in the bone marrow cells. Rytelo was only studied in patients without a del 5q cytogenetic abnormality. The classification system for MDS automatically classifies patients with the del 5q mutation as a separate unique subtype.

- One in three patients with MDS will progress to acute myeloid leukemia (AML). Risk of disease progression to AML and risk of mortality are assessed using the International Prognostic Scoring System (IPSS) or Revised International Prognostic Scoring System (IPSS-R). Both the IPSS and IPSS-R risk stratify patients with newly diagnosed MDS into risk categories based on blast percentage, number of cytopenias, and cytogenetic profile. The IPSS-R categorizes patients into 1 of 5 groups, from very low risk to very high risk using the patient's disease presentation including cytogenic groups, percentage of medullary blasts, hemoglobin, platelets, and absolute neutrophil count. Very low, low, or intermediate risk on the IPSS-R are conventionally defined as a risk score in the low or intermediate-1 range on the IPSS scale. Rytelo was only studied in patients classified as low or intermediate-1 risk disease using the IPSS.

- Safety and efficacy of Rytelo were evaluated in the IMerge trial, a randomized, double-blind, placebo-controlled, phase III study of 178 patients with low- to intermediate-1 risk MDS. Subjects were enrolled in the trial if they met the following criteria: RBC transfusion-dependent, defined as requiring at least 4 RBC units transfused over an 8 week period during the 16 weeks prior to randomization; pre-transfusion hemoglobin (Hgb) less than or equal to 9.0 g/dL; relapsed or refractory to ESA treatment or have an erythropoietin level greater than 500 mU/mL; an absolute neutrophil count (ANC) greater than or equal to 1.5×10^9/L independent of growth factor support; and platelets greater than or equal to 75×10^9/L independent of platelet transfusion. Refractory to ESAs was defined as at least one of the following: non-response or response that is no longer maintained to a prior ESA-containing regimen of either recombinant human erythropoietin > 40,000 IU/week for at least 8 doses or equivalent OR darbepoetin alpha > 500 µg every 3 weeks for at least 4 doses or equivalent. Patients were ineligible if they had del(5q) cytogenetic abnormality. The primary endpoint was 8 week and 24 week RBC transfusion independence (RBC-TI) defined as the proportion of subjects without any RBC transfusion during any consecutive 8 weeks or 24 weeks starting from study day 1 until subsequent anti-cancer therapy, if any. Median follow-up was 19.5 months (range: 12.0, 23.4) in the Rytelo group and 17.5 months (range: 12.1, 22.7) in the placebo

group. Rytelo demonstrated significantly higher rates of RBC-TI versus placebo for at least eight consecutive weeks (Rytelo 39.8% [95% CI: 30.9, 49.3]; placebo 15.0% [95% CI: 7.1, 26.6]; p-value < 0.001) and for at least 24 weeks (Rytelo 28.0% [95% CI: 20.1, 37.0]; placebo 3.3% [95% CI: 0.4, 11.5]; p-value < 0.001). RBC-TI was durable and sustained in the Rytelo treated population, with a median RBC-TI duration for 8-week responders and 24-week responders of approximately 1 year and 1.5 years, respectively.

- The current NCCN guidelines recommend ESAs as the preferred treatment in all patients and Reblozyl® as an alternative unless their serum erythropoietin is greater than 500 mU/mL in those with ring sideroblasts less than 15% or ring sideroblasts less than 5% with an SF3B1 mutation. Reblozyl is recommended first-line in instances where a patient presents with an erythropoietin greater than 500 mU/mL or a patient has ring sideroblasts greater than or equal to15% or ring sideroblasts greater than or equal to 5% with an SF3B1 mutation.

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Policy History		
#	Date	Change Description
1.1	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 08/01/2024	New Policy

Saphnelo™ (anifrolumab-fnia)
HCPCS: J0491

Background Information:

- Saphnelo is a type I interferon (IFN) receptor antagonist indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy. Efficacy has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus and use is not recommended in these situations.

    - Use of Saphnelo also has not been studied in combination with other biologic therapies and is not recommended.

    - Diagnosis of SLE was defined in the clinical trials by positive antinuclear antibody (ANA) titers (≥ 1:80), anti-double stranded DNA (dsDNA) antibodies, or anti-Smith (anti-Sm) antiboies upon study screening. The 2019 EULAR/ACR classification system for SLE allow ANA levels to be used as a qualifier for SLE, however, because ANA can elevate transiently and also be a marker for other diagnoses, a second confirmatory test must be done to confirm seropositivity. While other classification systems exist to define lupus, these systems do not ensure patients are seropositive as they only have to meet a certain number of criterion for diagnosis. Those criterion may or may not include positive tests for elevated ANA, anti-dsDNA titers, or anti-SM antibodies.

    - Saphnelo was studied in three multicenter, randomized, double-blind, placebo-controlled studies, MUSE, TULIP-1, and TULIP-2. All trials included patients who had positive ANA titers, dsDNA antibodies, or anti-SM antibodies at the time of study screening. Patients were stable and maintained on standard therapy throughout the study. TULIP-1's primary endpoint was the difference between the proportion of patients who achieved an SLE responder index-4 (SRI-4) response at week 52 with 300 mg Saphnelo versus placebo. TULIP-2's primary endpoint was the reduction in disease activity as measured by the BILAG-Based Composite Lupus Assessment (BICLA) scale. MUSE's primary endpoint was the percentage of patients achieving a SRI-4 response at week 24 with sustained reduction of oral corticosteroids. The SRI4 is a composite index requiring a 4-point reduction in the SELENA–SLEDAI score, no worsening (increase from baseline) in the physician's global assessment (on a 0 – 10-cm visual analog scale), and no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores at week 52 compared with baseline. The BICLA scale can register both partial and complete improvement within an organ system unlike the SRI-4 which requires complete resolution within a particular item to register change and cannot capture partial improvements. While TULIP-1 did not show statistically significant differences in the primary endpoint between the Saphnelo group and placebo, there were positive results seen in the secondary endpoints. Therefore, studies continued with TULIP-2 and MUSE both of who's primary endpoints showed statistical significance between treatment groups.

- The 2019 EULAR guidelines recommend use of hydroxychloroquine in all patients with the use of glucocorticoids to treat flares. The goal of therapy is for patients to get into remission or a state of low disease activity. If hydroxychloroquine use is still resulting in disease flare, use of immunosuppressants should be considered. The guidelines state Benlysta should be considered in patients who have failed hydroxychloroquine in combination with glucocorticoids and immunosuppressants. Guidelines have yet to be updated to include Saphnelo.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 10/09/2025	Annual review of policy. No changes were made to the criteria
1.2	Effective Date: 10/03/2024	Annual review of policy. No changes were made to the criteria
1.1	Effective Date: 10/12/2023	Annual review of policy. No changes were made to the criteria
1.0	Effective Date: 05/01/2023	New Policy

Simponi Aria® (golimumab)
HCPCS: J1602

Background Information:

- Simponi Aria (golimumab) is a tumor necrosis factor inhibitor (TNFi) indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA; in combination with methotrexate) or active ankylosing spondylitis, and for pediatric patients 2 years of age and older with active psoriatic arthritis or active polyarticular juvenile idiopathic arthritis.

- The use of Simponi Aria in combination with other biologic agents or targeted disease-modifying antirheumatic drugs is not recommended due to an increased risk of infection and a lack of robust safety and efficacy data to support combination use.

- Ankylosing Spondylitis

  - Axial spondyloarthritis, comprising ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (NRAS), is the main form of chronic inflammatory arthritis affecting the axial skeleton. Non-radiographic means that damage to the joints is not visible on X-ray. When changes to the vertebrae (the bones of the spine) or sacroiliac joints don't show any changes on an X-ray, that's known as NRAS. Once the joints are clearly affected on an X-ray, a person can be diagnosed with AS.

  - The 2019 American College of Rheumatology recommendations for AS and NRAS are similar. In adult patients who have active disease despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDS), treatment with tumor necrosis factor inhibitors (TNFi) are recommended. They do not recommend any particular TNFi as the preferred choice for the typical patient.

  - Cosentyx® (secukinumab) or Taltz® (ixekizumab) is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi, whereas for patients with a secondary nonresponse (i.e. those who relapse after an initial response) it may be beneficial to switch to a different TNFi rather than immediately switch to a different biologic class.

- Rheumatoid Arthritis

  - The 2021 American College of Rheumatology (ACR) Guidelines for the Treatment of Rheumatoid Arthritis (RA) established recommendations for the care of adult RA patients. The guidelines state that treatment decisions should follow a shared decision-making process and should be reevaluated within a minimum of 3 months based on the efficacy and tolerability of the DMARD(s) chosen.

- For the initial treatment of symptomatic RA, the guidelines strongly recommend the use of conventional synthetic DMARD (csDMARD) monotherapy in those who are DMARD-naive. csDMARD monotherapy is a less costly first line treatment option with an extensive safety record accompanied by well-documented clinical efficacy and a large body of clinical experience and familiarity among prescribers. csDMARDs in the guidelines refer to methotrexate (MTX), hydroxychloroquine, leflunomide (LEF), and sulfasalazine. Azathioprine, cyclosporine, minocycline, and gold were not included due to their infrequent use in RA and lack of new data since the prior guidelines were published. Oral MTX is recommended as the preferred initial DMARD for patients with moderate-to-high disease activity, and hydroxychloroquine is recommended as the preferred initial DMARD for patients with low disease activity.

- If disease activity remains moderate or high despite optimal dosing of methotrexate monotherapy, the use of dual therapy with methotrexate plus biologic DMARD (bDMARD; etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, sarilumab, rituximab) or targeted synthetic DMARD (tsDMARD; tofacitinib, baricitinib, upadacitinib) therapy is conditionally recommended over the use of triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine). The guidelines do not inform preference of bDMARD over tsDMARD therapy, or vice-versa, for use in combination with methotrexate. No one agent has been shown to be superior to another. The guidelines do acknowledge the emergence of safety signals for the JAK inhibitor class (tsDMARD), and state that further modification of this recommendation may be necessary as additional data are published.

- A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a pre-defined target (low disease activity or remission).

- Psoriatic Arthritis

  - PsA is a chronic inflammatory disease often associated with psoriasis. Psoriasis is an autoimmune disease affecting the skin, resulting in scaly red and white patches. These patches, called plaques, may appear anywhere on the body. The inflammation may also develop in the joints, which is classified as PsA. PsA occurs in up to 30% of patients with psoriasis, most commonly appearing between the ages of 30 and 50. PsA causes pain, stiffness, and swelling in and around the joints. If not properly treated, progressive joint damage may occur.

  - Per the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guideline for the treatment of psoriatic arthritis, all recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.

  - In treatment-naïve patients, oral systemic medications (OSMs), such as methotrexate, sulfasalazine, cyclosporine, and leflunomide, may be used in patients without severe psoriatic arthritis and without severe psoriasis. OSMs have robust longitudinal safety and efficacy data in patients with PsA. Maximal response to OSMs are most commonly achieved within 3 months of therapy.

- If PsA remains active despite OSM therapy, switching to a TNFi, an IL-17i, or an IL-12/23i biologic is recommended over switching to a different OSM; switching to a TNFi biologic over an IL-17i or IL-12/23i biologic is conditionally recommended in this scenario based on moderate quality evidence. The detailed recommendations for subsequent therapies can be found in the 2018 ACR/NPF guideline for the treatment of psoriatic arthritis.

- Juvenile Idiopathic Arthritis

- Juvenile idiopathic arthritis (JIA) defines a collection of inflammatory arthritides of unknown etiology. Onset is prior to 16 years of age with a minimum duration of 6 weeks and other potential causes of synovitis are excluded. JIA can be subdivided into polyarticular JIA and systemic JIA.

- pJIA is defined by the presence of more than 4 affected joints in the first 6 months of illness and comprises 20-30% of children with JIA. Therapy is directed toward treating the underlying inflammation and preventing JIA-associated complications and adverse effects of its treatment.

- The 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF) guideline for the treatment of JIA strongly recommends initial therapy for pJIA with a disease-modifying anti-rheumatic agent (DMARD) such as methotrexate (MTX) or leflunomide. MTX is conditionally recommended over leflunomide as it has a greater volume of data supporting its effectiveness compared to leflunomide and can be administered subcutaneously (recommended) or orally. The guidelines consider an adequate trial of a DMARD to be 3 months.

- If moderate or high disease activity persists despite DMARD use, the ACR/AF guidelines recommend biologic agents either in combination with a DMARD or as monotherapy in certain situations. Biologic agents FDA approved for pJIA in patients 2 years of age and older include Humira® (adalimumab), Enbrel® (etanercept), Actemra® (tocilizumab), Orencia® (abatacept), Simponi Aria® (golimumab), Xeljanz® (tofacitinib), and Xeljanz (tofacitinib) oral solution.

    - Of note, biologic therapy may be an appropriate initial therapy option in certain pJIA patients with risk factors and involvement of high-risk joints, high disease activity, and/or for those judged to be at high risk of disabling joint damage

- There is the most experience with TNFi (Humira, Enbrel, Simponi Aria) as initial biologic therapy; however, the preferred class of initial biologic is not specified in the guideline recommendations due to a lack of comparative data and the consideration that non-TNFi biologics may be preferred in certain patient-specific scenarios.

- If a TNFi is started as the initial biologic, switching to a non-TNFi (tocilizumab or abatacept) is recommended over switching to a second TNFi. An exception to this is for those who had a good initial response to the first TNFi.

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Policy History		
#	Date	Change Description
1.5	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Added that the member will self-administer Simponi unless clinically unable to do so
1.4	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.3	Effective Date: 12/14/2023	Annual review of criteria performed, no changes were made
1.2	Effective Date: 12/01/2022	Annual review of criteria performed, no changes were made

1.1	Effective Date: 12/09/2021	Removed FDA approved indications criteria Removed oral DMARD criteria for psoriatic arthritis indication Updated background information for rheumatoid arthritis to reflect 2021 guidelines; remaining guideline references within this section of the policy are up to date
1.0	Effective Date: 01/01/2021	New Policy

Skyrizi™ (risankizumab-rzaa)
HCPCS: Skyrizi SC: J3590; Skyrizi IV: J2327

Background Information:

- Skyrizi is an interleukin (IL)-23 antagonist indicated for the treatment of moderate-to-severe psoriasis in adults who are candidates for systemic therapy or phototherapy, for the treatment of active psoriatic arthritis in adults, for the treatment of moderately to severely active Crohn's disease in adults, and for the treatment of moderately to severely active ulcerative colitis in adults.

- Psoriasis

- Psoriasis is a chronic, painful, and life-altering immune-mediated disease which predominantly manifests with skin and joint involvement. Patients may also experience significant cardiovascular and psychological comorbidities. Approximately 2% of U.S. adults are affected by psoriasis (men and women equally), and it can occur at any age. Approximately 90% of psoriasis-affected patients have plaque psoriasis, which is characterized by well-defined round or oval plaques that vary in size and often coalesce. The severity of psoriasis is defined as: mild = less than 3% of body affected; moderate = 3-10% of body affected; and severe being more than 10% of the body affected.

- Per the 2020 Joint American Academy of Dermatology - National Psoriasis Foundation (AAD/NPF) guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures: topical corticosteroids provide a high efficacy and good safety option for patients with localized disease. They are generally recommended as first-line therapy. Choice of steroid potency may depend on severity, location, patient preference, and patient age, while the duration of treatment may vary with steroid potency, location and severity of disease often ranging from 2-12 weeks. Therapeutic regimens may include 2-4 weeks with a topical steroid applied twice daily, followed by a maintenance regimen where topical steroids are alternated with a steroid-sparing topical agent. Treatment with topical steroids for over 12 weeks is recommended under careful supervision by a physician.

- Per the 2019 Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with phototherapy: phototherapy serves as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications or simply seeking an adjunct to a failing regimen. Guidelines also state that the majority of patients with mild-to-moderate disease have adequate disease control with topical therapies and phototherapy alone.

- Per the Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with systemic nonbiologic therapies: many oral medications, including methotrexate, cyclosporine, and acitretin, have been used for decades to treat psoriasis, each with its own benefits and risks. Most work by targeting the immune system, whereas others, such as acitretin, work predominantly by decreasing keratinocyte

hyperproliferation, thus restoring the normal epidermal differentiation. Both methotrexate and cyclosporine are category A guideline recommendations for the treatment of moderate to severe psoriasis in adults and for severe, recalcitrant psoriasis, respectively. Studies examining the use of methotrexate and cyclosporine in psoriasis showed the primary efficacy endpoints met within 12-16 weeks. Acitretin is a category B guideline recommendation as monotherapy for plaque psoriasis, with full treatment response expected within 3-6 months.

- Per the 2019 Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with biologics: biologic agents, as monotherapy or combined with other topical or systemic medications, have a high benefit-to-risk ration. Tumor necrosis factor inhibitors (TNFi) and IL-12/IL-23, IL-23, and IL-17 products have a category "A" recommendation as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis. Guidelines do not recommend one product over another and note the similar efficacy seen across biologics within the same class. There are no published, robust studies to support the use of more than one biologic or targeted DMARD in combination.

- Psoriatic Arthritis

- Psoriatic arthritis (PsA) is a chronic inflammatory disease often associated with psoriasis. Psoriasis is an autoimmune disease affecting the skin, resulting in scaly red and white patches. These patches, called plaques, may appear anywhere on the body. The inflammation may also develop in the joints, which is classified as PsA. PsA occurs in up to 30% of patients with psoriasis, most commonly appearing between the ages of 30 and 50. PsA causes pain, stiffness, and swelling in and around the joints. If not properly treated, progressive joint damage may occur.

- Per the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guideline for the treatment of psoriatic arthritis, all recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.

- In treatment-naïve patients, oral systemic medications (OSMs), such as methotrexate, sulfasalazine, cyclosporine, and leflunomide, may be used in patients without severe psoriatic arthritis and without severe psoriasis. OSMs have robust longitudinal safety and efficacy data in patients with PsA. Maximal response to OSMs are most commonly achieved within 3 months of therapy.

- If PsA remains active despite OSM therapy, switching to a TNFi, an interleukin-17 inhibitor (IL-17i), or an IL-12/23i biologic is recommended over switching to a different OSM. In this scenario, a TNFi biologic is conditionally recommended over an IL-17i or IL-12/23i biologic based on moderate quality evidence. Additional treatment options include Xeljanz/Xeljanz XR (tofacitinib) and Orencia® (abatacept). Detailed recommendations regarding subsequent therapies can be found in the 2018 ACR/NPF guideline for the treatment of psoriatic arthritis.

- Crohn’s disease

- The 2018 American College of Gastroenterology guidelines establish therapeutic recommendations for patients with Crohn's disease (CD) based upon disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Current therapeutic approaches should be considered a sequential continuum to treat acute disease or induce clinical remission and then to maintain response/remission. In general, clinical evidence of improvement should be evident within 2 – 4 weeks and the maximal improvement should occur within 12 – 16 weeks. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease, have their medication dose adjusted in order to attempt to optimize therapy, or advance to treatment for moderate to severe disease according to their clinical status.

- Corticosteroids are used primarily for the treatment of flares of CD. Conventional corticosteroids are effective for reducing the signs and symptoms of active CD and induction of remission in patients with moderately to severely active CD. Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active disease. The guidelines recommend prednisone equivalent doses ranging from 40 to 60 mg per day. These doses are typically maintained for 1 –2 weeks and tapered at 5 mg weekly until 20 mg and then 2.5 –5 mg weekly. Once begun, care should be taken to ensure that corticosteroids are successfully discontinued, and steroid-sparing agents should be used.

- In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, mercaptopurine, azathioprine, and intramuscular or subcutaneous methotrexate are effective steroid-sparing agents and guideline recommended. Maximum effectiveness of these agents can be seen between 8 to 12 weeks from therapy initiation. Methotrexate is also recommended in combination with steroids as an effective treatment for moderately active steroid-dependent/resistant CD. Cyclosporine, tacrolimus, and mycophenolate are not recommended for treatment of CD.

- Biologics, such as TNFi's are recommended to treat CD that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. Guidelines also recommend the use of biologics in combination with immunosuppressants to help decrease the formation of antibodies against the biologic therapy. There are no robust, published studies to support use of biologic agents in combination

- The 2021 American Gastroenterological Association (AGA) guidelines include similar recommendations for the management of moderate-to-severe CD compared to the recommendations cited in the 2018 ACG guidelines. Both guidelines recommend corticosteroids over no treatment for induction of remission. Additionally, both guidelines recommend thiopurines, such as azathioprine or 6-mercaptopurine, as steroid-sparing agents for maintenance of remission. The AGA guidelines also recommend the same biologic agents cited in the ACG guidelines for treatment of CD, with the exception of Tysabri® (natalizumab), which the ACG suggests against use of due to its associated risk of progressive multifocal leukoencephalopathy (PML).

- Of note, the AGA guidelines conditionally recommend earlier introduction of biologic therapy prior to failure of corticosteroids; however, this recommendation is supported by a low level of clincial evidence. To date, no blinded randomized controlled trials (RCTs) have demonstrated the superiority of early introduction of biologic therapy compared to conventional induction therapy with corticosteroids followed by steroid-sparing therapy. The 2021 AGA guideline authors also acknowledge that earlier therapy with either combination immunomodulotor plus biologic therapy or biologic monotherapy may result in over-treating some patients and potentially exposing them to treatment-related risks and costs with limited benefit.

- Ulcerative Colitis

- UC and CD are two of the most common forms of inflammatory bowel disease (IBD). Both UC and CD are chronic, relapsing, remitting, inflammatory conditions of the gastrointestinal (GI) tract. UC only involves the large intestine as opposed to CD, which can affect any part of the GI tract from mouth to anus. CD can also affect the entire thickness of the bowel wall, while UC only involves the innermost lining of the large intestine. UC can present with symptoms of abdominal discomfort or loose bowel movements, including blood. The cause of UC or CD is not fully understood; however, research suggests that an interplay between environmental factors, genetics, and intestinal microbiota may contribute to the development of UC or CD. UC has an incidence of 9 to 20 cases per 100,000 persons per year. Its prevalence is 156 to 291 cases per 100,000 persons per year.

- The 2019 ACG guidelines and the 2020 AGA guidelines state therapeutic management in UC should be guided by the specific diagnosis, an assessment of disease activity, and disease prognosis. Treatment selection should be based not only on inflammatory activity but also on disease prognosis. Remission can be induced using a variety of medications, including oral 5-aminosalicyclic-acid (ASA), corticosteroids, or biologic agents. Thiopurines, such as azathioprine and mercaptopurine, can be used to maintain remission. The TNFi agents infliximab, adalimumab, and golimumab are effective for treatment of patients with UC. Treatment guidelines do not recommend the use of one agent over another as there have been no head-to-head trials comparing the agents to one another. Vedolizumab is another guideline recommended option in patients with moderately to severely active UC for induction of remission, and in patients with moderately to severely active UC who have previously failed anti-TNF therapy, for induction of remission.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/03/2024	Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria
1.1	Effective Date: 08/08/2024	Added ulcerative colitis indication
1.0	Effective Date: 01/01/2024	New Policy

Spevigo® (spesolimab-sbvo)
HCPCS: J1747

Background Information:

- Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening neutrophilic skin disease characterized by flares consisting of widespread eruptions of painful, sterile pustules. Patients with acute GPP may appear systemically ill and require hospital admission for adequate supportive care, and flares can be so disruptive to the system that they can trigger sepsis, cardiovascular complications, and renal failure. It is estimated that 1 out of every 10,000 people has GPP, and because it is so rare the condition is often under- or mis-diagnosed. Mortality ranges from 2% to 16% with deaths often attributed to septic shock and cardiorespiratory failure. Clinical course of GPP varies and can be relapsing with recurrent flares or persistent with intermittent flares. Flare frequency varies among patients and may be spontaneous or triggered by stress, infection, medication, or pregnancy.

- The European Rare and Severe Psoriasis Expert Network (ERASPEN) consensus statement on phenotypes of pustular psoriasis (2017) define GPP as macroscopically visible primary sterile pustules occurring on non-acral skin and not within psoriasis plaques. Per the ERASPEN, GPP may occur with or without systemic inflammation and with or without psoriasis vulgaris and should only be diagnosed when the condition has relapsed at least once or when it persists for more than 3 months. Of note, the National Psoriasis Foundation (NPF), in its 2023 consensus statement on GPP, indicates that our experience in the United States has shown that GPP can also occur on acral surfaces and may last fewer than three months. The ERASPEN also advises against counting pustules to measure GPP intensity as the spectrum can vary from discrete to confluent forms and notes there is an unmet need for development of a clinically validated standard to measure GPP severity.

- The goals of treatment of GPP are to improve skin manifestations, alleviate systemic symptoms, and minimize the risk for life-threatening systemic complications. There are no standard US or international guidelines for the treatment of GPP as high-quality data on the efficacy of treatments is lacking. Treatment options include systemic therapies, topicals, and phototherapy. Phototherapy has a delayed onset of action, and due to the widespread nature of GPP topicals may not be practical; therefore, these therapies are typically reserved as adjuncts to systemic therapy for the treatment of GPP.

- Japanese guidelines for the treatment of GPP (2018), a 2012 consensus statement on GPP from the NPF Medical Board, and joint guidelines on the treatment of psoriasis from the American Academy of Dermatology and NPF (2019, 2020) recommend an oral retinoid (e.g. acitretin), cyclosporine, methotrexate, and various biologics as potential systemic treatments for GPP. In the United States, these therapies are used off-label to treat GPP flares. The choice of systemic agent is based on disease severity and may differ between those with severe acute disease and those with stable disease. It should be noted that demonstration of efficacy with any of these agents is solely based on limited evidence from case reports and small, uncontrolled trials. No randomized controlled trials or other comparative studies have been done comparing treatment methods.

- A retinoid like acitretin is considered a first-line agent for GPP. Improvement (i.e., cessation of new pustule formation, initial improvement in other clinical signs) is typically seen within 7 to 10 days of initiating therapy, and a complete response is noted after 2 to 3 months of treatment. Methotrexate is an alternative, particularly for those intolerant to retinoids, with significant clinical improvement expected within 8 to 12 weeks of treatment. These agents can be continued for long-term maintenance treatment once the flare has resolved; however, due to their slow onset of action they are best suited for patients with less severe disease.

- More severe, acute GPP flares require rapid stabilization and improvement. For these patients, faster-acting drugs such as cyclosporine, infliximab, and interleukin (IL)-17 and IL -23 receptor antagonists are preferred. Cyclosporine and infliximab have a longer history of use compared to the IL-17 and IL-23 biologics, and both therapies are supported by the AAD, NPF, and Japanese guidelines. Marked improvement is often seen within the first few days of treatment with either of these agents. Some case reports with cyclosporine have demonstrated near-complete remission within 2 weeks, and Japanese guidelines cite the effects of infliximab as apparent within 24-48 hours in many cases and a clear effect often seen after 1 to 3 administrations. Once the flare has resolved, patients can be transitioned to alternative therapies like methotrexate or a retinoid for maintenance, or they can remain on infliximab. For those treated with cyclosporine, however, transitioning to another drug for maintenance is recommended due to side effect concerns with prolonged cyclosporine use.

- IL-17 inhibitors that have demonstrated benefit in small studies and case reports in GPP flares include secukinumab, ixekizumab and brodalumab. These drugs are approved to treat GPP in Japan and the Japanese guidelines support their use. Ustekinumab, an IL-23 inhibitor, has shown some efficacy in case reports for GPP; however, it is not approved for this indication in Japan and the Japanese guidelines suggest reserving use for those resistant to other treatment modalities. Dosing of interleukin receptor antagonists generally reflects doses recommended for plaque psoriasis; however, the optimal treatment regimen for GPP is unknown.

- In addition to select interleukin receptor antagonists, the tumor necrosis factor (TNF) inhibitors adalimumab and etanercept have demonstrated successful control of GPP in small numbers of patients. These drugs are considered second-line therapies for GPP flares by the 2012 NPF consensus and Japanese guidelines. Of note, there are reports of TNF inhibitors inducing pustular psoriasis, including GPP.

- Spevigo (spesolimab-sbvo) is the first and only therapy approved in the United States to treat GPP in adults and pediatric patients 12 years and older weighing at least 40 kg. It is an IL-36 inhibitor and is the first approved drug in this class. Loss-of-function mutations in the IL-36 receptor antagonist gene and other associated genes as well as overexpression of IL-36 cytokines in GPP skin lesions have been found in patients with GPP and support the role of the IL-36 pathway in the disease process.

- Spevigo for GPP flares was evaluated in the Phase II, randomized, multicenter, double-blind, placebo-controlled Effisayil-1 trial. Adults 18 to 75 years of age who had a history of GPP consistent with the ERASPEN diagnostic criteria and presenting with a GPP flare were randomly assigned in a 2:1 ratio to receive a single IV dose of Spevigo (n=35) or placebo (n=18). Patients were followed through week 12. The primary endpoint was

a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub-score of 0 (no visible pustules) at the end of week 1. The key secondary end point was a GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1. Scores range from 0 to 4, with higher scores indicating greater disease severity. Refer to Appendix A for a full description of the GPPGA.

- Trial participants were required to have a GPP flare of moderate to severe intensity as defined by the following:
  - A GPPGA total score of ≥ 3,
  - New or worsening pustules,
  - A GPPGA pustulation sub-score of ≥ 2, and

- ≥5% of body-surface area with erythema and the presence of pustules.

- At the end of week 1, 54% (19 of 35) patients in the Spevigo group met the primary endpoint compared to 6% (1 in 18) in the placebo group ($p<0.001$). Additionally, 43% (15 of 35) of patients treated with Spevigo showed clear/almost clear skin compared to 11% (2 of 18) in the placebo group ($p=0.02$).

- Patients in both groups were eligible to receive a single open-label dose of Spevigo on day 8 if the flare symptoms persisted as defined by a GPPGA total score ≥ 2 at the end of week 1, a clinician assessment of GPP severity based on a modified Physician Global Assessment, and a GPPGA pustulation sub-score of ≥2 at week 1.

- Both groups were also eligible to receive rescue treatment with a single dose of Spevigo in the case of flare reoccurrence after week 1, which was defined as an increase of ≥2 points in both the GPPGA total score and the pustulation sub-score after a GPPGA total score of 0 or 1 had been reached. It should be noted that only one rescue dose with Spevigo was allowed in the trial if a patient experienced a reoccurrence of a GPP flare after achieving clinical response to either Spevigo at day 1, placebo at day 1, escape medication, or an open-label dose of Spevigo at Day 8. Subsequent flares were treated with standard of care therapy per the physician's discretion.

- All patients in the trial were followed through 12 weeks. Effect on pustular and skin clearance was sustained over 12 weeks, with 84.4% who received Spevigo having no visible pustules after the 12 week trial duration, and 81.3% having clear/almost clear skin. Additionally, clearance was accompanied by clinically significant improvements in quality of life and symptoms such as pain and fatigue.

- For patients not experiencing a flare, the Phase IIb, randomized, double-blind, placebo-controlled Effisayil-2 trial evaluated the safety and efficacy of Spevigo for SC administration in patients 12 to 75 years of age with a documented history of GPP consistent with the ERASPEN diagnostic criteria, a history of at least 2 GPP flares of moderate to severe intensity with new or worsening pustulation, and a GPPGA score of 0 or 1. Patients already receiving GPP treatment prior to randomization were required to discontinue treatment and must have had a history of flaring while on concomitant treatment for GPP or in case of dose reduction or discontinuation of these concomitant medications. Patients who were not on concomitant GPP treatment at randomization were required to have had at least two moderate to severe GPP flares in the past year, with at least one displaying evidence of either fever and/or elevated C-reactive protein and/or elevated white blood count, and/or asthenia, and/or myalgia.

    - Participants (n=123) were randomized 1:1:1:1 to one of four treatment arms: Spevigo 600 mg SC loading dose followed by 300 mg SC every 4 weeks (high dose); Spevigo 600 mg SC loading dose followed by 300 mg SC every 12 weeks (medium dose); Spevigo 300 mg SC loading dose followed by 150 mg SC every 12 weeks (low dose); or matched placebo.

    - The primary endpoint was the time to first GPP flare up to week 48, defined by a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub-score > 2 and an increase in GPPPGA total score by > 2 from baseline.

    - Results demonstrated that treatment with SC Spevigo (high dose) significantly reduced the risk of GPP flares by 84% over 48 weeks compared to placebo; by week 48, 3 (10%) of 30 patients in the high dose group experienced GPP flares compared to 16 (52%) of 31 patients in the placebo group.

- To treat a GPP flare, Spevigo is recommended as a single IV infusion. If flare symptoms persist, an additional dose may be administered one week after the initial dose. For patients not experiencing a flare, Spevigo is recommended as a subcutaneous (SC) injection for maintenance to prevent flare occurrence. Should a patient experience a flare during treatment with SC Spevigo, the flare can be treated with IV Spevigo.

- Spevigo fills an unmet need as the only FDA-approved treatment for GPP; however, the off-label alternatives that have historically been used can also be used for both GPP flares and prevention and provide more cost-effective alternatives by comparison. There is no literature comparing the safety and efficacy of Spevigo to that of alternatives to determine differences in clinical efficacy. The NPF strongly advocates for timely access to FDA-approved therapies for GPP like Spevigo as delays may increase mortality risk in patients with more rapidly progressing GPP. Ultimately, the choice of therapy is dependent on the individual patient and may differ between those with severe acute disease and those with stable disease.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made

1.2	Effective Date: 06/06/2024	Updated to add FDA approved indication criteria and criteria for members with GPP not experiencing a flare and authorization period and renewal criteria specific to Spevigo SC
1.1	Effective Date: 10/12/2023	Annual review of criteria performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Spinraza® (nusinersen)
HCPCS: J2326

Background Information:

- SMA is a severe, inherited progressive neuromuscular disease that causes devastating muscle atrophy and disease-related complications in approximately 4 to 10 per 100,000 live births. SMA is caused by a mutation in the survival motor neuron 1 (SMN1) gene that results in a deficiency of SMN protein. People have a "backup" copy of this gene called SMN2 that produces low levels of SMN protein. SMA varies in severity with four different types that inversely correlates to the number of SMN2 copies a person has. The type of SMA a person has is based on function and age of onset. Type 1 is the most severe type of SMA and the most common. It affects 6 out of every 10 children with SMA. Those with Type 1 have the fewest number of SMN2 copies (usually 2 or fewer). Type 1 patients have an age of onset usually between 0-6 months, and as the natural history of those with Type 1 SMA progresses the children will never be able to sit unsupported. Life expectancy of untreated Type 1 patients is less than 2 years old. Type 2 patients usually present around 7-18 months of age and will have the ability to sit, but never stand. The majority of SMA Type 2 patients have 3 copies of SMN2. Type 3 SMA patients present after 18 months of age and usually are able to stand and walk. About 51% of the patients with SMA Type 3 have 3 copies of SMN2 while 46% have 4 copies of SMN2. Although there is an inverse correlation between severity of disease and number of SMN2 copies, diagnoses of type is not solely based on number of SMN2 copies.

- Spinraza is an antisense oligonucleotide that alters splicing of SMN2, increasing full-length, SMN (survival motor neuron) mRNA protein production. This is thought to improve motor function and achievement of motor milestones in patients and delays the progression in presymptomatic patients. Thus, early treatment is thought to result in the greatest potential benefit.

- Although approved to treat all SMA patients regardless of type and age:

    - Spinraza has only been studied in patients with SMA types 1-3 which make up approximately 95% of all SMA cases. SMA type 4 is usually later onset (often after age 30) and patients are able to achieve motor milestones and maintain mobility throughout life.

    - There is a lack of clinical data supporting the benefits of Spinraza on fully ventilator dependent patients.

    - Therefore, the safety and efficacy of Spinraza has not been confirmed outside of the above patient population.

- SMA patients' motor function and ability are monitored in a variety of ways, including but not limited to Bayley Scales of Infant and Toddler development (BSID), Motor Function Measure 32 (MFM-32), Hammersmith Infant Neurological Exam (HINE), Hammersmith Functional Motor

Scale Expanded (HFMSE), Revised Upper Limb Module (RULM) Test (non-ambulatory patients), Six-Minute Walk Test (6MWT) (ambulatory patients only) and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND).

- There is currently no data supporting co-administration of Spinraza with other SMA therapies, in those who have received gene therapy for SMA, and in patients requiring invasive ventilation. The pivotal clinical studies did not include this patient population, therefore the safety and efficacy of Spinraza is unknown in this patient population at this time.

- Bridging therapy with either Evrysdi or Spinraza prior to the use of Zolgensma can be appropriate in young patients with elevated anti-AAV9 antibodies. Elevated titers are not common (~13%) in SMA patients. Those that do have titers can get it from the placenta at birth from mothers who have acquired them. Just like other maternal antibodies passed on to children, these antibodies diminish over time. Bridging therapy allows patients to start therapy without delay, and waits for the titers to naturally diminish. Scientists have stressed the importance of treating SMA as early as possible, and suggested that patients with elevated antibodies be given disease-modifying therapies that work through different mechanisms — Spinraza (nusinersen) or Evrysdi (risdiplam) — as "bridge treatments" until able to receive Zolgensma.

- Provider portals are used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 08/07/2025	Annual Review of Medical Policy
1.5	Effective Date: 08/08/2024	Updated to prevent concurrent use with other SMA therapies including gene therapy, but to allow the use of Spinraza prior to Zolgensma with regard to bridging therapy
1.4	Effective Date: 04/11/2024	Annual Review of Medical Policy
1.3	Effective Date: 04/06/2023	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 06/10/2021	Removed upper age limit criteria. Added not to be used in combination with other SMA therapies
1.0	Effective Date: 01/01/2021	New Policy

Syfovre™ (pegcetacoplan)
HCPCS: J2781

Background Information:

- Geographic atrophy is an advanced and severe form of dry age-related macular degeneration (AMD). It is caused by the gradual breakdown of light-sensitive cells in the macula resulting in the growth of irreversible lesions in the retinal pigment epithelium (RPE). GA progression causes a gradual loss of visual function. Symptoms include scotomas, difficulty recognizing faces, decreased reading speed, impaired dark adaptation, low luminance deficit (LLD), impaired contrast sensitivity, and difficulty driving at night. More than half of all patients with GA will experience significant impairment of everyday vision, and about 20% of patients will develop severe vision loss with visual acuity of 20/200 or worse.

- The exact cause of GA is unknown but it is thought the disease is the result of a multifactorial process. The most significant risk factors include age and family history with genetics playing a role in disease development. It is thought errors found in the genes of the complement cascade may cause inflammation making the eye more susceptible to GA. Smoking and a higher body mass index are also risk factors.

- Diagnosis is made by an ophthalmologist during a dilated exam and/or with retinal imaging. In a dilated exam, geographic atrophy appears as a patch of retina that's missing its dark melanin pigment. Imaging techniques including retinal color photographs, optical coherence tomography (OCT), or autofluorescence photographs can also be used to detect GA.

- Syfovre is a C3 complement inhibitor indicated for the treatment of GA secondary to AMD. It is the first FDA approved therapy for GA. It targets the complement overactivation generating GA progression, preventing lesion growth, and reducing the likelihood of severe disease.

- GA can be secondary to other conditions outside of AMD. Those include Stargardt disease, cone rod dystrophy, or toxic maculopathies like plaquenil maculopathy. Syfovre has only been studied in patients with GA secondary to dry AMD and therefore should not be used to treat GA secondary to other conditions. If the patient has multiple eye conditions requiring treatment, such as wet and dry AMD, it is appropriate to treat both conditions simultaneously.

- Syfovre has not been studied in patients with a visual acuity worse than 20/320. Use should be limited to those patients with visual acuity equal to or better than 20/320.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/03/2024	Annual review – no changes to the criteria at this time
1.1	Effective Date: 10/12/2023	Updated to include criteria not allowing use with other medications for the treatment of GA
1.0	Effective Date: 08/01/2023	New policy

Tecartus™ (brexucabtagene autoleucel)
HCPCS: Q2053

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

    - Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) and Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

    - Safety and efficacy were established in the ZUMA-2 trial, a single-arm, open-label, multicenter phase II study of 74 adult patients with relapsed or refractory mantle cell lymphoma. Patients had received up to 5 prior lines of therapy, including an anti-CD20 antibody, either an anthracycline- or bendamustine-containing chemotherapy regimen, and a Bruton's tyrosine kinase (BTK) inhibitor. Three patients experienced manufacturing failure, one died of progressive disease, and one withdrew from the study prior to lymphodepleting chemotherapy. One patient received lymphodepleting chemotherapy but did not receive Tecartus due to ongoing active atrial fibrillation. Tecartus was administered as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T-cells/kg. The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously given on the fifth, fourth, and third day before Tecartus. Patients with prior allogeneic HSCT, any active central nervous system malignancy, ECOG performance status of 2 or greater, absolute neutrophil count less than 1,000/µL, platelet count < 75,000/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection were excluded. The primary endpoint was objective response rate to therapy which was 87%, including 37 patients who had complete response (62%) and 15 who had a partial response (25%). The median time to response was 28 days with median duration of response not yet being reached.

- Safety and efficacy for use in acute lymphoblastic leukemia were established in the ZUMA-3 trial, a multicenter, phase I/II trial of 55 adult patients with relapsed or refractory ALL. Patients must have had documentation of CD19 positive disease and if they were Philadelphia chromosome positive, must have been intolerant to, had a contraindication to, or have failed 2 lines of tyrosine kinase inhibitor therapy. Patients with prior allogeneic SCT within 100 days of therapy, any active central nervous system malignancy, ECOG performance status of 2 or greater, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, diagnosis of Burkitt's lymphoma, grade 2 to 4 graft-versus-host disease, or active serious infection were excluded. The primary endpoint is overall complete remission rate. In the study, 70.9% presented with a complete remission rate. The median duration of response was 12.8 months and the median overall survival (OS) was 18.2 months.

- Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

    - While use of Tecartus has not been established in patients with a creatinine clearance of less than 60 mL/minute, other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other CAR-T therapies support their use in these patients, Tecartus should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 ml/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.

    - While use of Tecartus has not been established in patients with an alanine aminotransferase of greater than 2.5 times the upper limit of normal (ULN), other CAR-T therapies have been studied in subjects with an alanine aminotransferase of up to 5 times the ULN and the CTCAE recommendations have set 5 times the ULN as the cutoff for grade 2 adverse reactions. As the classification system uses 5 times the ULN and other CAR-T therapies have data supporting use in this patient population, Tecartus should be tolerated in these patients as well. As there is no data to support administration of CAR-T at levels higher than 5 times the ULN, therapy should not be given to patients not meeting that threshold.

    - The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. While Tecartus has only been studied in patients with a LVEF greater than or equal to 45%, there is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Tecartus should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.

- A provider portal that is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

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Policy History		
#	Date	Change Description
1.5	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 08/04/2022	Updated to align criteria across all CAR-T policies

1.3	Effective Date: 04/14/2022	Updated to remove CD19 requirement as NCCN guidelines state CAR-T can work without being positive for CD19 disease
1.2	Effective Date: 12/09/2021	Updated to include new indication of ALL
1.1	Effective Date: 08/12/2021	New policy. This policy replaces previously approved criteria that was embedded in Chimeric Antigen Receptor-T Cell Class policy which will be retired. The criteria was also updated to add preliminary criteria for use in ALL
1.0	Effective Date: 01/01/2021	New Policy

Tecelra® (afamitresgene autoleucel)
HCPCS: Q2057

Background Information:

- Tecelra is a melanoma-associated antigen A4 (MAGE-A4)-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

- Specific peptide enhanced affinity receptor (SPEAR), T-cell therapy is a type of treatment the utilizes the body's own immune system to fight cancer. Autologous T-cells are transduced with a lentiviral vector to create Tecelra which expresses MAGE-A4-specific affinity-enhanced T-cell receptors (TCRs) on the surface of the cells. The engineered TCRs recognize an HLA-A*02-restricted MAGE-A4 peptide resulting in antigen-specific activation of Tecelra, T-cell proliferation, cytokine secretion, and killing of MAGE-A4/HLA-A*02-expressing synovial sarcoma cells.

- SPEAR T-cell therapy has not been studied when given following prior treatment with any SPEAR T-cell therapy or following any other genetically-modified T-cell therapy.

    - Safety and efficacy were evaluated in the SPEARHEAD-1 trial, an open-label, non-randomized, phase 2 study of 44 patients with metastatic or unresectable synovial sarcoma who had received prior systemic therapy with either doxorubicin and/or ifosfamide and whose tumor expressed the MAGE-A4 tumor antigen. MAGE-A4 expression was defined as greater than or equal to 2+ staining in greater than or equal to 30% of the cells by immunohistochemistry. Patients needed to be HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P, and HLA-A*02:06P allele positive. Subjects with an HLA-A*02:05P allele were not included in the trial. The study excluded patients with an ECOG score of 1 or greater, a creatinine clearance of less than or equal to 40 mL/minute, alanine aminotransferase greater than 2.5 times upper limit of normal, and left ventricular ejection fraction less than 40%. Patients were also excluded if absolute neutrophil count less than 1000 cells/mm^3 and platelet count less than 75,000/mm^3. Patients were required to have measurable disease. The primary endpoint was overall response rate (ORR). The ORR was 43.2% (95% CI: 28.4, 59.0) with a complete response rate of 4.5% and partial response rate of 38.6%. The median duration of response was 6 months (95% CI: 4.6, not reached). Among patients who were responsive to the treatment, 39% had a duration of response of 12 months or longer.

- A provider portal platform is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.2	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 10/03/2024	New policy - this criteria replaces previously approved preliminary criteria
1.0	Effective Date: 10/01/2024	New Policy

Tecvayli™ (teclistamab-cqyv)
HCPCS: J9380

Background Information:

- Tecvayli is a bispecific BCMA-directed/CD3 T-cell engager 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.

- Safety and efficacy were evaluated in the MajesTEC-1 study, a single-arm, multi-cohort, open-label, phase I/II trial of 110 patients with relapsed or refractory multiple myeloma who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Subjects had not received prior BCMA-targeted therapy. About 78% of patients had received at least 4 prior lines of therapy, with a median number of 5. The study excluded patients who had stroke, seizure, allogeneic stem cell transplantation (SCT) within the past 6 months, an ECOG performance score of 2 or higher, known active CNS involvement or clinical signs of meningeal involvement of multiple myeloma, or active or documented history of autoimmune disease. The primary endpoint was overall response rate (ORR). The median time to first response was 1.2 months (range: 0.2 to 5.5 months). With a median follow-up of 7.4 months among responders, the estimated duration of response (DOR) rate was 90.6% (95% CI: 80.3%, 95.7%) at 6 months and 66.5% (95% CI: 38.8%, 83.9%) at 9 months. The ORR was 61.8% (95% CI: 52.1%, 70.9%).

- Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

- Due to the risk of cytokine release syndrome and neurological toxicities, the step-up doses of Tecvayli are required to be administered in an inpatient setting.

- Tecvayli has not been studied when given following prior treatment with Tecvayli or following any other bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager therapy.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 10/03/2024	Updated to remove the requirements of active disease, liver function, kidney function, no uncontrolled infection, no detectable hepatitis B or C viral load, cardiac function, no stroke event within 6 months of therapy administration, no pulmonary disease requiring oxygen dependence, no seizures within 6 months of therapy administration, and no active autoimmune disease. Also added the requirements that the patient has not had an allogenic stem cell transplant within the past 6 months and no autologous stem cell transplant within the past 12 weeks
1.1	Effective Date: 10/12/202	Updated to align criteria with the other bispecific BCMA directed CD3 T-cell engager therapies including adding liver enzymes tests to be less than or equal to 3 times the ULN, creatinine clearance greater than or equal to 40 mL/min, left ventricular ejection fraction greater than 40%, no autoimmune disease, and removed the requirement ensuring there is no HIV infection
1.0	Effective Date: 08/23/2023	New Policy

Tepezza™ (teprotumumab-trbw)
HCPCS: J3241

Background Information:

- Thyroid eye disease is a complex orbital inflammatory disease, which can be sight threatening, debilitating, and disfiguring. It is caused by antibodies directed against receptors in the thyroid cells and also on the surface of the cells behind the eyes. Muscles and fatty tissues behind the eye become inflamed leading to proptosis (eye bulging), strabismus (misalignment of the eyes), and diplopia (double vision) and in some cases can lead to blindness. Risk factors for the disease include female gender, middle age, and smoking. Active TED lasts for up to three years with the disease only responding to pharmacotherapy while it is active and inflammation is ongoing.

- Tepezza is an insulin-like growth factor-1 receptor antagonist indicated for the treatment of thyroid eye disease (TED).

- Goals of treatment in thyroid disease consists of achieving a euthyroid state and symptom management. The majority of patients with thyroid eye disease have mild to moderate disease and require primarily supportive care with ocular lubrication, topical cyclosporine, and lifestyle modification, such as, smoking cessation, sodium restriction, and sunglasses.

- The current mainstay of treatment for moderate to severe thyroid eye disease is oral or intravenous corticosteroids. Treatment can be initiated at doses of oral prednisone 30 mg daily for four weeks or methylprednisolone 500 mg once weekly for weeks 1 to 6, then 250 mg once weekly for weeks 7 to 12 with cumulative dose 4.5 to 5 g over 12 weeks. The European Thyroid Association recommends initial treatment with IV glucocorticoids for moderate-to-severe, active orbitopathy, citing several studies that suggest it is more efficacious and associated with fewer side effects than oral therapy. Similar trials have not been performed in the United States, where initiation with oral glucocorticoids remains the most common first-line treatment. Treatment for thyroid eye disease should start in the early months of the active inflammatory phase, as treatment becomes less effective as the disease progresses.

- There are no clinical head to head studies that compare steroids and Tepezza for the treatment TED. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy state Tepezza's incorporation into routine clinical practice is currently limited by the lack of comprehensive long-term efficacy and safety data and the absence of head-to-head comparison trials with intravenous glucocorticoids.

- Safety and efficacy were evaluated in the OPTIC trials, two multicenter, randomized, double-masked, placebo-controlled trials of 171 patients with thyroid eye disease. Patients were required to have active, moderate to severe thyroid eye disease with significant symptoms, including at least one of the following: lid retraction of greater than or equal to 2 mm, moderate or severe soft-tissue involvement, proptosis of greater than or equal to 3 mm, and periodic or constant diplopia. Patients were also required to have a clinical activity score (CAS) greater than or equal to 4

and symptoms less than 9 months from the onset of thyroid eye disease. All patients were euthyroid or with mild hypothyroidism or hyperthyroidism, defined as free thyroxine (T4) and free triiodothyronine (T3) levels less than 50% above or below the normal limits for the testing laboratory. Patients with previous orbital irradiation or surgery for thyroid eye disease were not allowed. The primary endpoint in the first trial was a composite endpoint of reduction of greater than or equal to 2 points in the CAS and a reduction of greater than or equal to 2 mm in proptosis. The primary endpoint in the second trial was a reduction in proptosis of greater than or equal to 2 mm. In both trials, significantly more patients treated with teprotumumab demonstrated less symptoms of thyroid eye disease than patients treated with placebo.

- In 2023, results from a randomized, double-masked, placebo-controlled, phase 4 clinical trial evaluating Tepezza for the treatment of adults with chronic TED and low CAS scores became available. The phase 4 trial evaluated patients with an initial diagnosis of TED between two to 10 years (mean duration of 5.2 years; SD 1.77) and low levels of disease activity (mean CAS of 0.4; SD 0.49), whereas the prior pivotal trials that formed the basis of the original FDA approval of Tepezza evaluated patients with disease duration of nine months or less and higher levels of disease activity. At week 24, the primary endpoint was met and patients treated with Tepezza achieved a statistically significant reduction in proptosis from baseline compared to those receiving placebo.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 06/08/2023	Updated to remove criteria specific to disease activity in support of the updated FDA indication
1.2	Effective Date: 12/01/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 12/09/2021	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 11/01/2021	New Policy

Tezspire™ (tezepelumab-ekko)
HCPCS: J2356

Background Information:

- Tezspire is a thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody (IgG2λ), indicated:
    - For the 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.
    - For the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP)
- TSLP is a key epithelial cytokine in allergy and asthma pathophysiology and is overexpressed in asthmatic patients. Once released, TSLP drives multiple downstream innate and adaptive immune responses.
- Severe asthma
    - Severe asthma is uncontrolled despite adherence with maximally optimized high dose inhaled corticosteroids/long-acting beta agonists (ICS/LABA), or that requires high dose ICS/LABA to prevent it from becoming uncontrolled.
    - Asthma affects 25 million Americans with 1.6 million ER visits, 180,000 hospitalizations, and 3,500 deaths each year. Severe asthma afflicts 5 to 10 percent of the asthma population but drives the majority of the morbidity and costs of the disease.
    - Add-on treatments for severe asthma include LAMAs, leukotriene receptor antagonists (LTRA), low-dose azithromycin (adults), and biologic agents for severe allergic or severe type 2 asthma. Type 2 inflammation is found in a majority of people with severe asthma and is characterized by the production of cytokines such as interleukin (IL). The Global Institute for Asthma (GINA) 2022 guidelines have the following recommendations for add-on biologic therapy for severe asthma:
        - Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4–5 treatment (Evidence A).

    - Add-on anti-IL-5/5R treatment (subcutaneous mepolizumab for patients aged ≥6 years; intravenous reslizumab for ages ≥18 years; or subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4–5 treatment. Efficacy data for mepolizumab in children 6–11 years are limited to one very small open label uncontrolled study.

    - Add-on anti-IL-4Rα treatment (subcutaneous dupilumab) for patients aged ≥6 years with severe eosinophilic/Type 2 asthma, or for adults or adolescents requiring treatment with maintenance OCS.

    - Add-on anti-thymic stromal lymphopoietin (anti-TSLP) (subcutaneous tezepelumab): for patients aged ≥12 years with severe asthma (Evidence A).

- Per the GINA 2022 guidelines, a trial of at least 4 months of an add-on biologic therapy is recommended before assessing response.

- Eosinophilic asthma is a sub-phenotype of severe asthma characterized by elevated sputum and blood eosinophil levels as well as increased asthma severity, atopy, late-onset disease, and steroid refractoriness.

- A peripheral blood eosinophil count is an indirect way to estimate airway inflammation. A blood eosinophil count ≥ 300 cells/microliter may help to predict asthmatics who are at increased risk for exacerbations in the next year. Furthermore, a count-response relationship exists between blood eosinophil counts and asthma-related outcomes. The European Respiratory Society/American Thoracic Society guidelines from 2020 suggest that treatment of severe asthma be guided by clinical criteria and biomarkers such as blood eosinophil levels or fractional exhaled nitric oxide (FeNO), rather than by clinical criteria alone. In addition, it also suggests that a blood eosinophil count cut-off point of ≥ 150 cells/microliter can be used to guide anti-IL5 therapy initiation in adult patients with severe asthma and a history of prior asthma exacerbations.

- Type 2 inflammation is found in a majority of people with severe asthma and is characterized by production of cytokines such as interleukin and can also include immunoglobulin E (IgE)-mediated events involving mast cells and basophils (in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells). Anti-IgE monoclonal antibodies reduce the levels of circulating IgE and inhibit the binding of IgE to mast cells to prevent activation of the allergic cascade and decrease inflammation.

    - IgE levels of >30 but <700 IU/mL for patients 12 years of age and older and IgE levels >30 but <1,300 IU/mL for patients between the ages of 6 to <12 years were used in the efficacy data from Xolair clinical trials and showed where Xolair was most effective.

- Clinical reasons a patient may be unable to self-administer Tezspire include:

    - Patient or caregivers are unable to perform subcutaneous (SC) injections with proper technique.

- Member requires monthly medical support from the physician.

- Chronic rhinosinusitis with nasal polyps

  - Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic disease of the upper airway predominantly driven by Type 2 inflammation and characterized by polyps that obstruct the sinuses and nasal passages. Current treatment options are intranasal corticosteroids (INCS), systemic corticosteroids, and surgery, all with suboptimal efficacy and/or high recurrence rates after treatment. Patients may experience severe nasal obstruction with breathing difficulties, nasal discharge, reduced or loss of sense of smell and taste, and facial pain or pressure.
  - Persistent symptoms of CRSwNP have a substantial adverse impact on patients' health-related quality of life, a composite that includes reduced productivity and activities of daily living, inability to enjoy food, lack of sleep and fatigue.

  - Per the Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyps (Journal of Allergy and Clinical Immunology; 2023) in people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation based on low certainty of evidence), and the guideline panel suggests biologics rather than no biologics in people with CRSwNP (conditional recommendation based on moderate certainty of evidence.)

  - The approval in CRSwNP was based on efficacy and safety data from the Phase III WAYPOINT trial, which enrolled 408 patients with severe, uncontrolled CRSwNP. Tezspire significantly reduced nasal polyp severity, nearly eliminated the need for surgery, and significantly reduced systemic corticosteroid use versus placebo, with a safety profile consistent with prior studies.

References:

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4. PRNewswire press release; FDA approves Tezspire™ (tezepelumab-ekko) in the U.S. for severe asthma (prnewswire.com) accessed December, 2021.
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Policy History		
#	Date	Change Description
1.3	Effective Date: 12/04/2025	Update to include new indication for chronic rhinosinusitis with nasal polyps

1.2	Effective Date: 12/12/2024	Updated in combo with other DMARD verbiage to align with other biologic policies.
1.1	Effective Date: 12/14/2023	Specific step therapy is now “Medicare only” criteria.
1.0	Effective Date: 05/01/2023	New Policy

Tocilizumab Products
Actemra® (tocilizumab) J3262
Avtozma® (tocilizumab-anoh) J3590
Tocilizumab-aazg Q5135
Tofidence™ (tocilizumab-bavi) Q5133
Tyenne™ (tocilizumab-aazg) Q5135

Background Information:

- Tocilizumab is an interleukin-6 inhibitor (IL-6i) available as the innovator product Actemra and its biosimilars Avtozma, Tofidence, and Tyenne.
    - Actemra is indicated for RA, GCA, pJIA, sJIA, CRS, SSc-ILD, and COVID-19. It is available for both subcutaneous (SC) and intravenous (IV) administration. For CRS and COVID-19, only the IV formulation is approved for use whereas only the SC formulation is approved for SSc-ILD. Either Actemra formulation may be used for all other indications.
    - In contrast to the innovator product, Avtozma, Tofidence, and Tyenne are approved for RA, pJIA, sJIA, GCA and COVID-19. Tyenne also carries an additional indication for CRS. Tofidence is only available in an IV formulation, whereas Avtozma and Tyenne are available in IV and SC formulations.
- Tocilizumab has not been studied in combination with other biologic disease-modifying agents such as tumor necrosis factor inhibitors, interleukin receptor antagonists, anti-CD20 monoclonal antibodies, and selective co-stimulation modulators due to an increased risk of infection and increased immunosuppression. As such, use of tocilizumab products in combination with other biologic agents is not recommended.
    - Rheumatoid Arthritis

- The 2021 American College of Rheumatology (ACR) Guidelines for the Treatment of Rheumatoid Arthritis (RA) established recommendations for the care of adult RA patients. The guidelines state that treatment decisions should follow a shared decision-making process and should be reevaluated within a minimum of 3 months based on the efficacy and tolerability of the DMARD(s) chosen.
- For the initial treatment of symptomatic RA, the guidelines strongly recommend the use of conventional synthetic disease-modifying antirheumatic drug (csDMARD) monotherapy in those who are DMARD-naive. csDMARD monotherapy is a less costly first line treatment option with an extensive safety record accompanied by well-documented clinical efficacy and a large body of clinical experience and familiarity among prescribers. csDMARDs in the guidelines refer to methotrexate (MTX), hydroxychloroquine, leflunomide (LEF), and sulfasalazine.

Azathioprine, cyclosporine, minocycline, and gold were not included due to their infrequent use in RA and lack of new data since the prior guidelines were published. Oral MTX is recommended as the preferred initial DMARD for patients with moderate-to-high disease activity, and hydroxychloroquine is recommended as the preferred initial DMARD for patients with low disease activity.

- If disease activity remains moderate or high despite optimal dosing of methotrexate monotherapy, the use of dual therapy with methotrexate plus biologic DMARD (bDMARD; etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, sarilumab, rituximab) or targeted synthetic DMARD (tsDMARD; tofacitinib, baricitinib, upadacitinib) therapy is conditionally recommended over the use of triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine). The guidelines do not inform preference of bDMARD over tsDMARD therapy (or vice-versa) for use in combination with methotrexate. No one agent has been shown to be superior to another. The guidelines do acknowledge the emergence of safety signals for the JAK inhibitor class (tsDMARD), and state that further modification of this recommendation may be necessary as additional data are published.

- A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a pre-defined target (low disease activity or remission).

- Tocilizumab is indicated for treating adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. Tocilizumab may be used as monotherapy or concomitantly with other non-biologic DMARDs as an IV infusion or as a subcutaneous injection for the treatment of RA.

  - Polyarticular Juvenile Idiopathic Arthritis

- Juvenile idiopathic arthritis (JIA) defines a collection of inflammatory arthritides of unknown etiology. JIA onset is prior to 16 years of age with a minimum duration of 6 weeks and other potential causes of synovitis are excluded. JIA can be subdivided into pJIA and sJIA.

- pJIA is defined by the presence of more than 4 affected joints in the first 6 months of illness and comprises 20-30% of children with JIA. Therapy is directed toward treating the underlying inflammation and preventing JIA-associated complications and adverse effects of its treatment.

- The 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF) guideline for the treatment of JIA strongly recommends initial therapy for pJIA with a DMARD such as MTX or LEF. MTX is conditionally recommended over LEF as it has a greater volume of data supporting its effectiveness compared to LEF and can be administered subcutaneously (recommended) or orally. The guidelines consider an adequate trial of a DMARD to be 3 months.

- If moderate or high disease activity persists despite adequate DMARD use, the ACR/AF guidelines recommend biologic agents either in combination with a DMARD or as monotherapy in certain situations. Biologic agents FDA approved for pJIA in patients 2 years of age and older include Humira® (adalimumab), Enbrel® (etanercept), tocilizumab, Orencia® (abatacept), Simponi Aria® (golimumab), Xeljanz® (tofacitinib), Xeljanz (tofacitinib) oral solution, and Cimzia® (certolizumab pegol).

    - Of note, biologic therapy may be an appropriate initial therapy in pJIA patients with risk factors and involvement of high-risk joints, high disease activity, and/or for those judged to be at high risk of disabling joint damage.

- There is the most experience with tumor necrosis factor inhibitors (TNFi; Humira, Enbrel, Simponi Aria) as initial biologic therapy; however, the preferred class of initial biologic is not specified in the guideline recommendations due to a lack of comparative data and the consideration that non-TNFi biologics may be preferred in certain patient-specific scenarios. If a TNFi is started as the initial biologic, switching to a non-TNFi (tocilizumab or Orencia) is recommended over switching to a second TNFi. An exception to this is for those who had a good initial response to the first TNFi.

– Systemic Juvenile Idiopathic Arthritis and Adult Onset Still's Disease

- sJIA is a rare and distinct subset of JIA. It accounts for 4-15% of JIA and is defined as arthritis in > 1 joint for at least 6 weeks duration in a child age < 16 years with or preceded by a fever of at least 2 weeks duration that is documented to be daily for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis. This condition can occur in adulthood with similar features and is referred to as AOSD when diagnosed in patients 16 years of age and older.

- AOSD and sJIA may also be complicated by macrophage activation syndrome (MAS), a secondary hemophagocytic syndrome that can be life-threatening and requires urgent recognition and treatment. MAS presents with fevers, high ferritin levels, cytopenias, elevated liver enzyme, low fibrinogen levels, and high triglyceride levels. Regardless of MAS presence at presentation, careful monitoring is necessary as MAS can occur at any point during the disease course.

- The inflammatory process underlying sJIA and AOSD appears to be distinct from other categories of JIA, with interleukin (IL)-1 and IL-6 playing a central role. The goal of therapy focuses on prompt control of active inflammation and symptoms and prevention of disease- and or treatment-related morbidities like growth disturbances, joint damage and functional limitations.

- Treatment recommendations vary depending on the presence of MAS. The 2021 ACR guideline for pharmacologic management of oligoarthritis, TMJ arthritis, and sJIA in children recommend the following for the treatment of sJIA:

- Classes of pharmacologic interventions addressed in the recommendations include:
- Any NSAIDs at therapeutic dosing
- Traditional DMARDs (i.e., methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, calcineurin inhibitors (cyclosporin A, tacrolimus))
- Biologics (i.e., tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol), abatacept, IL inhibitors (tocilizumab, anakinra, canakinumab))
- Glucocorticoids, including any oral or intravenous agent, or intraarticular triamcinolone acetonide or triamcinolone hexacetonide.
- In the presence of MAS, an IL-1 or IL-6 inhibitor (no preferred agent) and/or systemic glucocorticoids are recommended for initial treatment. If residual arthritis is present, a traditional DMARD may be added or treatment can be switched to a different biologic agent (no preferred agent).
- In sJIA without MAS, the guidelines recommend monotherapy with an IL-1 or IL-6 inhibitor (no preferred agent) and/or a brief trial of scheduled NSAIDs. The guidelines do not provide a recommended duration of initial use for NSAIDs. Traditional DMARDs are strongly recommended against as initial monotherapy as they are minimally effective at controlling systemic features of sJIA alone. Glucocorticoids are also conditionally recommended against as initial monotherapy; however, they may be used to help control systemic and joint manifestations of sJIA until an IL-1 or IL-6 inhibitor can be started. If a patient experiences an incomplete response or intolerance to first-line treatment, switching to an alternative IL-1 or IL-6 inhibitor is recommended (no preferred agent).
- Regardless of the presence of MAS, if a patient responds to initial treatment but residual arthritis is present, a traditional DMARD or switch to a different biologic (no preferred agent) is recommended.
- Ultimately, treatment is continued and the patient monitored until the sJIA becomes inactive, at which point it is recommended that the patient taper and stop biologics and/or glucocorticoids.

- Tocilizumab and Ilaris® (canakinumab; IL-1 inhibitor) are FDA approved for the treatment of sJIA in patients 2 years of age and older, while Ilaris is the only drug approved for the treatment of AOSD. There are no guidelines for treating AOSD; however, literature recommends a similar

treatment approach to sJIA. The use of tocilizumab in AOSD is supported by a small, randomized trial and several case reports and case series that have shown efficacy in patients with AOSD with both the intravenous and subcutaneous formulations. Tocilizumab's efficacy in patients with sJIA also serves as additional evidence to support its use in AOSD.

- Cytokine Release Syndrome

  - CRS is an acute systemic inflammatory syndrome that is characterized by fever with or without multiple organ dysfunction occurring in response to chimeric antigen receptor (CAR)-T cell therapy, therapeutic antibodies and haploidentical allogeneic hematopoietic cell transplantation (HCT). The incidence of CRS varies based on the causative treatment and underlying malignancy. It most often occurs following targeted cellular immunotherapy for B cell acute lymphoblastic leukemia/lymphoma (ALL/LBL), non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukemia (CLL), and multiple myeloma (MM), and is less common following immunotherapy with bispecific antibodies and in the treatment of solid tumors.

  - The systemic inflammatory reaction that occurs with CRS involves increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells; IL-6 appears to have a central role in CRS pathophysiology. The resulting manifestation of the CRS inflammatory response includes fever, which may be accompanied by fatigue, headache, rash, diarrhea, arthralgia, and myalgia. Mild CRS may progress to a more severe form, which may include hypotension, hypoxia, and uncontrolled systemic inflammatory response with circulatory collapse, vascular leakage, peripheral and/or pulmonary edema, renal failure, cardiac dysfunction, and multiorgan system failure. Neurologic manifestations may also develop in severe CRS, including aphasia, altered level of consciousness, impaired cognitive skills, motor weakness, seizures, and cerebral edema.

  - Diagnosis is made by clinical presentation and the temporal relationship to the triggering immune therapy. CRS typically begins within 1-14 days after CAR-T cell therapy with resolution within a few days to 2-3 weeks post CAR-T infusion. CRS diagnosis requires a fever (≥38°C) at onset, with or without hypotension, hypoxia, and/or other end-organ dysfunction in the hours to days after treatment with immune therapy like CAR-T. Due to variability of laboratory findings in CRS, laboratory studies are not required for diagnosis though they may be beneficial for differential diagnosis.

  - The severity of CRS is graded differently based on the causative immune therapy; literature includes diverse grading scales as there are various grading scales proposed for CRS. CAR-T therapy grading proposed by the American Society for Transplantation and Cellular Therapy (ASTCT) is based on the degree and type of interventions required for patient management.

- Grade 1: Temperature ≥38°C and no hypotension and no hypoxia (defined by a requirement for supplemental oxygen to correct an oxygen deficit vs. a specific level of oxygen saturation). Patients may have malaise, myalgias, or arthralgias, but the severity of these constitutional symptoms does not affect the grade of CRS

- Grade 2: Temperature ≥38°C plus hypotension that does not require vasopressors and/or hypoxia that requires low-flow nasal cannula (≤6 L/minute or blow-by oxygenation). See the notes below regarding aspects of the management of hypotension and hypoxia that may affect grading.

- Grade 3: Temperature ≥38°C plus hypotension that requires one vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow nasal cannula (≥6 L/minute), facemask, non-rebreather mask, or Venturi mask that is not attributable to any other cause.

- Grade 4: Temperature ≥38°C plus hypotension that requires multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation and mechanical ventilation). Intubation for reasons other than hypoxia alone does not meet criteria for Grade 4 CRS.

- The National Comprehensive Cancer Network (NCCN) guidelines for management of immunotherapy-related toxicities (version 1.2022) recommends treatment with Actemra (tocilizumab) for patients with Grade 2, 3 or 4 CRS related to CAR-T cell therapies either as monotherapy or in conjunction with IV corticosteroids. NCCN recommends considering Actemra treatment for prolonged (> 3 days) Grade 1 CRS in patients with significant symptoms, comorbidities, and/or are elderly.

- Actemra is FDA approved for treating severe or life-threatening CRS due to CAR-T cell therapy in patients 2 years of age and older. If there is no improvement after the first dose, the dose may be repeated in 8 hours for a maximum of 3 doses in 24 hours and 4 doses total. The need for subsequent dosing must be assessed after each dose.

- CAR-T therapy is currently only administered as one dose per lifetime; it has not been studied in patients who received prior treatment with any CAR-T therapy or other genetically modified T-cell therapy. As such, the use of Actemra for CRS related to CAR-T is limited to a one-time treatment.

- The FDA REMS program regulates CAR-T cell products in the United States. REMS guidelines should be consulted for specific details of CRS management as guidelines for treating CRS associated with CAR-T cell therapy varies according to the specific product.

- Giant Cell Arteritis

- GCA (also known as Horton disease, cranial arteritis, and temporal arteritis) is the most common systemic vasculitis in North America, affecting adults over 50 years of age with a peak incidence between ages 70 and 79. Symptoms and signs of GCA typically results from vascular inflammation of the small extracranial branches of the carotid arteries; however, the disease is systemic and may involve the aorta and large arteries, leading to aneurysms of the thoracic and abdominal aorta ischemic symptoms in the extremities, respectively.

- Manifestations of GCA vary between patients and may be transient or fluctuating. Systemic symptoms are frequent and may include fever, fatigue and weight loss. Diagnosis of GCA should be considered in patients over 50 years old complaining of or found to have one or more of the following symptoms, the significance of which is heightened if a patient has a current or prior diagnosis of polymyalgia rheumatica:

    - New headache

    - Abrupt onset of visual disturbances, in particular transient monocular visual loss

    - Jaw claudication

    - Unexplained fever or anemia

    - Elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)

- The most significant complication of GCA is vision loss, which most frequently arises from cranial arteritis, a major phenotype of GCA. Approximately 25-50% of untreated patients who present with vision loss in one eye will develop bilateral blindness, and once visual impairment due to GCA is established, it is rarely reversible. Another concern is subclinical involvement of the aorta and large arteries (large vessel GCA), which occurs frequently and may result in aortic aneurysm and dissection.

- The 2021 ACR/Vasculitis Foundation Guideline for GCA and Takayasu Arteritis recommends temporal artery biopsy as the gold standard for GCA diagnosis; scheduling of the biopsy, however, should not interfere with treatment initiation when there is a high likelihood of GCA as a delay can put patients at risk of significant complications, particularly vision loss. In patients with a negative biopsy but high GCA suspicion, the guideline conditionally recommends noninvasive vascular imaging of the large vessels with clinical assessment to aid in diagnosis. The diagnostic procedure of choice for suspected large vessel GCA is advanced imaging of the torso (i.e. CT, MRI, PET scan).

- High dose glucocorticoid treatment (typically prednisone for 2-4 weeks) followed by a slow oral glucocorticoid taper is typically the mainstay of therapy for GCA and should be instituted promptly if a diagnosis of GCA is strongly suspected, especially in the event of recent or threatened vision loss. The initiation of IV or oral glucocorticoids is determined based on the presence of visual symptoms/loss or critical cranial ischemia.

Prompt glucocorticoid treatment reduces the risk of sight loss to less than 1% in patients with intact vision at time of treatment initiation. Glucocorticoid effectiveness in GCA is well established by decades of clinical experience, producing prompt improvement of signs and symptoms generally within 24 to 48 hours of treatment initiation.

- The 2021 guideline conditionally recommends the use of glucocorticoids combined with tocilizumab or other non-glucocorticoid immunosuppressants over oral glucocorticoids alone for patients with newly diagnosed GCA; however, the guideline ultimately defers to the treating physician and the patient's clinical condition, values, and preferences in making the decision to treat with glucocorticoid monotherapy or combination therapy. Once a patient is in clinical remission, the oral glucocorticoids can be tapered.

- Relapses may occur and are most common at prednisone doses less than 20 mg/day; these are treated with increases in the glucocorticoid dose appropriate to the relapse, and/or the addition of a nonglucocorticoid immunosuppressants like tocilizumab or methotrexate. The optimal duration of therapy for GCA is not well established given the variable presentation and duration of symptoms and may extend from one to multiple years. The 2021 guideline panel takes the position that the duration of therapy should be guided by the patient and emphasized minimizing the use of glucocorticoids as much as possible due to glucocorticoid toxicity; however, the panel recognized that longer-term use may be needed in select patients to avoid relapses and flares.

- Potential toxicities of glucocorticoids are of concern in patients of advanced age, with comorbid conditions (e.g., preexisting diabetes mellitus, osteoporosis, significant obesity), and utilizing glucocorticoid therapy for extended periods of time. The prevalence of significant glucocorticoid-related adverse events correlates with increased patient age and cumulative glucocorticoid dose. Based on the patient population affected by GCA and the prolonged exposure to glucocorticoids, early implementation of glucocorticoid-sparing agents like tocilizumab may be preferred to minimize toxicity risk.

- Tocilizumab is FDA approved for the treatment of GCA in adults based on safety and efficacy data from pivotal trials that evaluated tocilizumab for both new-onset and relapsing GCA. For the treatment of GCA, tocilizumab is recommended in combination with a tapering course of glucocorticoids; monotherapy with Actemra may be continued following glucocorticoid discontinuation.

  - Systemic sclerosis-associated interstitial lung disease

  - SSc-ILD is a rare autoimmune disease affecting about 75,000 people in the U.S. It is characterized by thickening, hardening, and scarring of the skin and caused by the accumulation of excess collagen in the skin and internal organs, such as the heart, lungs, kidneys, and intestinal tract, leading to organ damage. An estimated 80% of patients have ILD due to the buildup of scar tissue and inflammation in the lungs. ILD is a progressive disease that can significantly impact lung function.

- Mycophenolate and cyclophosphamide are considered standard of care as initial therapy as supported by numerous clinical trials and the European League Against Rheumatism (EULAR) guidelines for SSc (updated in 2017). Mycophenolate is often preferred in practice as it has comparable benefit to cyclophosphamide but has a better toxicity profile. Ofev® and more recently Actemra subcutaneous injection received FDA approval for this indication and are options for patients who are not candidates for mycophenolate or cyclophosphamide.

- The approval of Actemra was based on the results of a Phase III, placebo-controlled trial. The trial did not meet its primary goal of a change on a standard skin fibrosis measurement called the modified Rodnan Skin Score (mRSS). However, based on a post hoc subgroup analysis, a benefit was apparent in patients with confirmed SSc-ILD. Analyses found that these Actemra-treated patients, relative to those on placebo, had a smaller decline in mean forced vital capacity (FVC).

- COVID-19

- On December 21, 2022, Actemra was approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). This approval is for adults aged 18 and older only. There is still an Emergency Use Authorization in place for use of Actemra for treatment of COVID-19 in hospitalized patients aged 2-17.

- Actemra comes in 2 formulations: an IV infusion formulation and a subcutaneous injection formulation. The FDA approval for COVID-19 only pertains to the IV formulation as the medication should not be self-administered in the hospital. The recommended dosage of Actemra for adult patients with COVID-19 is 8 mg/kg administered via a 60-minute IV infusion.

- The National Institutes of Health (NIH) COVID-19 Treatment Guidelines recommend oral Olumiant® (baricitinib) or IV Actemra in addition to dexamethasone in patients who are hospitalized requiring high-flow nasal cannula (HFNC) oxygen or noninvasive ventilation (NIV), or in patients who are hospitalized requiring ECMO or mechanical ventilation (MV).

- The primary outcome in the RECOVERY trial was 28-day mortality in those receiving Actemra compared to usual care alone. The rate ratio was 0.85; (95% CI 0.76-0.94; p=0.0028) demonstrating that Actemra was statistically significant in reducing 28-day mortality compared to usual care alone. Additionally, among patients who were not receiving invasive mechanical ventilation at baseline in the RECOVERY trial, patients on Actemra were less likely to reach the composite endpoint of invasive mechanical ventilation or death. The risk ratio was 0.84; (95% CI, 0.77-0.92; p <0.0001).

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Policy History		
#	Date	Change Description
2.0	Effective Date: 08/07/2025	Added tocilizumab-aazg unbranded biosimilar to the policy
1.9	Effective Date: 05/27/2025 P&T Date: 04/10/2025	Updated to add Avtozma and criteria requiring the member to self-administer unless clinically unable to do so
1.8	Effective Date: 10/03/2024	Added "for the same indication" to the not to be used in combination with other biologics or targeted DMARDs criteria
1.7	Effective Date: 04/11/2024	Added biosimilar Tyenne to the policy
1.6	Effective Date: 12/14/2023	Changed policy name from Actemra to Tocilizumab Products Policy due to approval of biosimilar

		Updated to add Tofidence, FDA approved indications criteria, and criteria to allow coverage for biosimilar products for FDA labeled indications of the innovator product
1.5	Effective Date: 04/06/2023	Removed DMARDs from sJIA and AOSD step options, added SSc-ILD authorization and renewal criteria, and changed CRS initial authorization period to 60 days to align with PA60 legislation
1.4	Effective Date: 04/14/2022	Updated giant cell arteritis criteria and supporting information to allow use of SC or IV formulation per updated labeling
1.3	Effective Date: 12/09/2021	Removed FDA approved indications criteria
1.2	Effective Date: 04/08/2021	Updated to include criteria for new indication of SSc-ILD
1.1	Effective Date: 02/04/2021	Addition of criteria for coverage of Still's disease, including AOSD
1.0	Effective Date: 01/01/2021	New Policy

Trastuzumab Class Policy
Herceptin® (trastuzumab) J9355
Hercessi™ (trastuzumab-strf) Q5146
Herzuma® (trastuzumab-pkrb) Q5113
Kanjinti™ (trastuzumab-anns) Q5117
Ogivri™ (traztuzumab-dkts) Q5114
Ontruzant® (trastuzumab-dttb) Q5112
Trastuzumab-dttb J3590
Trastuzumab-pkrb J3590
Trazimera™ (trastuzumab-qyyp) Q5116

Background Information:

- Herceptin and its biosimilars are anti-HER2 monoclonal antibodies that bind to the HER2 receptor and inhibit proliferation of tumor cells that overexpress the receptor. Both breast and gastric cancers can be positive for the HER2 receptor. Herceptin and the trastuzumab biosimilars have been studied in these tumor types and are guideline recommended for use. When used as adjuvant therapy, trastuzumab should be given for a total of 52 weeks of therapy. When used in metastatic disease, treatment should continue indefinitely until unacceptable toxicity or disease progression. Trastuzmab products are not effective against tumors that do not overexpress the HER2 receptor.

- The National Comprehensive Cancer Network (NCCN) 2025 Breast Cancer guidelines and NCCN 2025 Gastric Cancer guidelines support the use of the American Society of Clinical Oncology (ASCO)/College of American Pathologist (CAP) HER2 testing guidelines. The guidelines define tumors as HER2-positive when they meet any of the following: a single probe average HER2 copy number greater than or equal to 6.0 signals/cell, a dual-probe HER2/CEP17 ratio greater than or equal to 2.0, or a dual-probe HER2/CEP17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 6.0 signals/cell.

- NCCN guidelines category 1 recommendations are based on high levels of evidence and uniform concensus that the recommendation is appropriate. Category 2A recommenations are based on a lower level of evidence but still have NCCN uniform concensus the recommenations are appropriate. Category 2B and lower recommendtions are based on low levels of evidence and do no have concensus the recommendation is appropriate, therefore, these treatment regimens should only be used when all other options have been exhausted.

- Where guidelines recommend trastuzumab to be used in combination with other agents as part of a treatment regimen it should be administered as such. Studies have been completed to support use as combination therapy in these scenarios. There are situations where use as a single agent is warranted, for instance, in breast cancer following multiple modality anthracycline therapy. When recommended, trastuzumab can be given as monotherapy.

- NCCN guidelines state an FDA approved biosimilar can be substituted for Herceptin. The guidelines do not specify what biosimilars are appropriate for a specific tumor type which allows for use of any of the biosimilars to be used for any indication the innovator product is FDA approved for.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 02/12/2026	Updated to include trastuzumab-dttb
1.4	Effective Date: 08/07/2025	Updated to include trastuzumab-pkrb
1.3	Effective Date: 06/05/2025	Annual review – no changes to the criteria at this time
1.2	Effective Date: 06/06/2024	Updated to include Hercessi
1.1	Effective Date: 04/11/2024	Annual review – no changes to the criteria at this time
1.0	Effective Date: 06/01/2023	New Policy

Tremfya® IV (guselkumab)
HCPCS: J1628

Background Information:

- Tremfya (guselkumab) is an interleukin-23 inhibitor (IL-23i) with the following indications:
  - Adults and pediatric patients 6 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis who are candidates for systemic therapy of phototherapy
  - Adults and pediatric patients 6 years of age and older who also weigh at least 40 kg with active psoriatic arthritis
  - Adults with moderately to severely active ulcerative colitis
  - Adults with moderately to severely active Crohn's disease (CD)

- Tremfya is available as a subcutaneous (SC) injection and an intravenous (IV) infusion. The IV formulation is only indicated for the induction phases of ulcerative colitis and CD, whereas the SC formulation is indicated for plaque psoriasis, psoriatic arthritis, and both the induction and maintenance phases of ulcerative colitis and CD.

- Per the prescribing information, Tremfya may be administered alone or in combination with traditional DMARDs (e.g., methotrexate) for psoriatic arthritis. There is no robust clinical evidence supporting the safety and efficacy of Tremfya used in combination with other biologic agents or targeted DMARDs (e.g., Janus kinase (JAK) inhibitors).

- Clinical reasons a patient may be unable to self-administer Tremfya include:
  - Patient or caregivers are unable to perform subcutaneous injections with proper technique
  - Member requires monthly medical support from the physician

- Ulcerative colitis

- The 2019 ACG guidelines and the 2020 AGA guidelines for ulcerative colitis (UC) state therapeutic management in UC should be guided by the specific diagnosis, an assessment of disease activity, and disease prognosis. Treatment selection should be based not only on inflammatory activity but also on disease prognosis.

- Remission can be induced using a variety of medications, including, oral 5-aminosalicylates (5-ASA), corticosteroids, or biologic agents. In patients with mild to moderately active disease, treatment with 5-ASA therapy has proven to be safe and efficacious for induction. Recommended dosing is 2 grams per day of oral 5-ASA or at least 1 gram per day of rectal 5-ASA with improvement usually seen within 4 weeks. A typical treatment course may be up to 8 weeks.

- Oral steroids are recommended for induction for patients with severe disease or those who did not respond to 5-ASA therapy. The typical starting doses of oral prednisone are 40 – 60 mg per day, and clinical response is expected within 5 – 7 days of treatment. A typical treatment course with oral prednisone is 14 days. The duration of systemic corticosteroids should be as short as possible with early initiation of steroid-sparing therapy. The speed of the taper should be guided by clinical symptoms, cumulative steroid exposure, and onset of action of alternate therapies. Those unable to taper off of 10-20 mg of prednisone per day without relapsing are considered steroid dependent. Use systemic corticosteroids for maintenance of remission is not recommended.

- Thiopurines, such as azathioprine and mercaptopurine, can be used to maintain remission. Guidelines recommend use of thiopurines over no medication or corticosteroids for maintenance therapy. Thiopurines are slow acting with maximum effectiveness of these agents being seen between 8 to 12 weeks from therapy initiation. They do not induce remission in moderately to severely active ulcerative colitis. Similarly, methotrexate is not an effective induction agent for induction or maintenance of remission.

- In patients with moderate to severe disease, TNFi, Entyvio® (vedolizumab), and ustekinumab are recommended for the induction and maintenance of remission. For patients with moderate to severe disease in remission, guidelines do not recommend biologic monotherapy over thiopurine monotherapy. Thiopurines can be used as adjunctive therapy for reducing immunogenicity against biologic therapy and are guideline recommended.

- Crohn's disease

- The 2018 ACG guidelines establish therapeutic recommendations for patients with CD based upon disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Current therapeutic approaches should be considered a sequential continuum to treat acute disease or induce clinical remission and then to maintain response/remission. In general, clinical evidence of improvement should be evident within 2 – 4 weeks and the maximal improvement should occur within 12 – 16 weeks. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease, have their medication dose adjusted in order to attempt to optimize therapy, or advance to treatment for moderate to severe disease according to their clinical status.

- Corticosteroids are used primarily for the treatment of flares of CD. Conventional corticosteroids are effective for reducing the signs and symptoms of active CD and induction of remission in patients with moderately to severely active CD. Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active disease. The ACG guidelines recommend prednisone equivalent doses ranging from 40 to 60 mg per day. These doses are typically maintained for 1 –2 weeks and tapered at 5 mg weekly until 20 mg and then 2.5 –5 mg weekly. Once begun, care should be taken to ensure that corticosteroids are successfully discontinued, and steroid-sparing agents should be used.

- In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, mercaptopurine, azathioprine, and intramuscular or subcutaneous methotrexate are effective steroid-sparing agents and guideline recommended. Maximum effectiveness of these agents can be seen between 8 to 12 weeks from therapy initiation. Methotrexate is also recommended in combination with steroids as effective for treatment of moderately active steroid-dependent/resistant CD. Cyclosporine, tacrolimus, and mycophenolate are not recommended for treatment of CD.

- Biologics, such as TNFi are recommended to treat CD that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. The ACG guidelines also recommend the use of biologics in combination with immunosuppressants to help decrease the formation of antibodies against the biologic therapy. There are no robust, published studies to support use of biologic agents in combination.

- The 2021 AGA guidelines include similar recommendations for the management of moderate-to-severe CD compared to the recommendations cited in the 2018 ACG guidelines. Both guidelines recommend corticosteroids over no treatment for induction of remission. Additionally, both guidelines recommend thiopurines, such as azathioprine or 6-mercaptopurine, as steroid-sparing agents for maintenance of remission. The AGA guidelines also recommend the same biologic agents cited in the ACG guidelines for treatment of CD, with the exception of Tysabri® (natalizumab), which the ACG suggests against use of due to its associated risk of progressive multifocal leukoencephalopathy (PML).

Of note, the AGA guidelines conditionally recommend earlier introduction of biologic therapy prior to failure of corticosteroids; however, this recommendation is supported by a low level of clinical evidence. To date, no blinded randomized controlled trials (RCTs) have demonstrated the superiority of early introduction of biologic therapy compared to conventional induction therapy with corticosteroids followed by steroid-sparing therapy. The 2021 AGA guideline authors also acknowledge that earlier therapy with either combination immunomodulator plus biologic therapy or biologic monotherapy may result in over-treating some patients and potentially exposing them to treatment-related risks and costs with limited benefit.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 12/05/2025	Added FDA approved weight criterion based on expanded indications for psoriatic arthritis and psoriasis to now include pediatrics 6 years and older weighing at least 40 kg
1.2	Effective Date: 06/05/2025	Updated to require subcutaneous products to be self-administered unless clinically unable to do so
1.1	Effective Date: 04/10/2025	Updated to include the new Crohn's disease indication
1.0	Effective Date: 01/20/2025	New Policy

Trogarzo® (ibalizumab-ulyk)
HCPCS: J1746

Background Information:

- Trogarzo is indicated for use in combination with other ARTs for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant (MDR) HIV-1 infection failing their current antiretroviral regimen. It is a humanized IgG4 monoclonal antibody that blocks the entry of HIV-1 through binding to CD4.

- The indication, along with specific criteria on defining treatment resistance and failure, reflects the patient population that was included in the clinical trial that lead to its approval. Therefore, use outside of this specific patient population is not recommended as the safety and efficacy has not been established.

- The evidence of efficacy for Trogarzo is based on one small, open-label, phase 3 trial in 40 patients. The primary outcome evaluated was the proportion of patients obtaining at least a 0.5 log10 reduction in HIV-1 RNA viral load compared to baseline. There was a statistically significant greater proportion of patients achieving at least a 0.5 log10 viral load reduction after seven days of treatment than at baseline (83% vs. 3%, respectively). A decrease of at least 0.5 log10 HIV-1 RNA viral load is considered clinically significant in MDR HIV-1 as this delays clinical progression.

- More than 25 approved antiretroviral drugs in multiple classes are available to design combination antiretroviral treatment (ART) regimens. Treatment always consist of drugs from multiple categories. Viral failure can occur for many reasons including development of drug resistance, suboptimal adherence and drug intolerance/toxicity prompting a new antiretroviral regimen to be designed.

- Guidelines from the U.S. Department of Health and Human Services (2024) and International Antiviral Society–USA Panel (2024) state:
  - Virologic failure is a viral load that is persistently greater than or equal to 200 copies/mL because this level of viremia often leads to drug resistance.
  - In patients with virologic failure, it is crucial to provide continuous adherence support before and after ART regimen changes.
  - Designing a new regimen for patients who are experiencing treatment failure should always be guided by ART history and results from current and past resistance testing.
  - Patients with MDR HIV-1 who have few treatment options their new regimen should include at least two, and preferably three, fully active agents, including those with novel mechanisms of action (ex: ibalizumab, fosternsavir, lenacapavir). If less than 3 fully active drugs, include as many fully active drugs as possible, along with potentially partially active drugs.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 10/09/2025	Annual Review Added updated IAS-USA guidelines (2024) and DDHS Panel guidelines (2024). Updated pricing table and pipeline information.
1.4	Effective Date: 10/03/2024	Annual review – no changes to the criteria
1.3	Effective Date: 10/12/2023	Annual review – no changes to the criteria
1.2	Effective Date: 10/06/2022	Updated to remove specific prescriber requirement per NCQA recommendations and loosen requirement to allow for documented resistance of at least one antiretroviral medication from three different classes without specifying which classes must be trialed
1.1	Effective Date: 10/07/2021	Annual review – no changes to the criteria
1.0	Effective Date: 01/01/2021	New Policy

Tzield™ (teplizumab-mzwv)
HCPCS: J9381

Background Information:

- Type 1 diabetes (T1D) is an autoimmune disorder in which the pancreas is unable to produce enough insulin due to autoimmune destruction of pancreatic beta cells. The CDC estimates that about 5-10% of the diabetic population has T1D which typically develops in children, teenagers, and young adults; however, T1D can happen at any age. Markers of immune destruction of the beta cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD65, and autoantibodies to tyrosine phosphatases I-2 and IA-2B. At least one, and usually more, of these autoantibodies are present in 85-90% of individuals when fasting hyperglycemia is first detected.

- In T1D the rate of beta cell destruction is variable and the patient may go through distinct stages before progressing to symptomatic disease requiring insulin. According to the American Diabetes Association's (ADA) Standards of Medical Care in Diabetes (2025), there are three distinct stages of T1D.

- Stage 1 is characterized by autoimmunity, normoglycemia, and is pre-symptomatic. Multiple (at least two) islet autoantibodies are typically present and the patient exhibits no evidence of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). 5-year risk of developing symptomatic T1D is about 44% overall but varies depending on a number of factors.

- Stage 2 exhibits autoimmunity, dysglycemia (i.e., abnormal glucose tolerance), and is also pre-symptomatic. In this stage, islet autoantibodies are present (usually multiple) and dysglycemia is demonstrated by IFG (i.e., fasting plasma glucose of 100-125 mg/dL) and/or IGT (i.e., 2-hour plasma glucose of 140-199 mg/dL on oral OGTT). A hemoglobin A1c of 5.7-6.4% or $\geq$ 10% increase in A1c may also be diagnostic of this stage. At stage 2, there is an approximately 60% risk of developing a clinical diagnosis of T1D by 2 years and approximately 75% risk within 5 years.

- Stage 3 is also characterized by autoimmunity, but at this point the patient has progressed to overt hyperglycemia and is symptomatic. Autoantibodies may become absent at this stage and the patient can be diagnosed with T1D by standard criteria outlined in the ADA's Standards of Medical Care.

- The presence of IFG as defined in Stage 2 and/or IGT as defined in Stage 2 and/or an A1c of 5.7-6.4% define prediabetes, a term for those whose glucose levels do not meet criteria for diabetes yet demonstrate abnormal carbohydrate metabolism. Patients with prediabetes are at relatively high risk for future development of diabetes. The 2025 ADA Standards of Medical Care recommend fasting plasma glucose, 2-hour plasma glucose during a 75-gram OGTT, and A1c as equally appropriate for screening for prediabetes. When using OGTT as a screening tool, adequate carbohydrate intake of at least 150 grams per day should be assured prior to testing; fasting and carbohydrate restriction can falsely elevate glucose level with an oral glucose challenge.

- The 2025 ADA Standards of Medical Care recommend screening for pre-symptomatic T1D using screening tests to detect autoantibodies to insulin, GAD, islet antigen 2, or ZnT8 as an option for first-degree family members of a proband with T1D. The development and persistence of multiple islet autoantibodies is considered a risk factor for clinical diabetes and may serve as an indication for screening for Stage 2 T1D.

- Delay of development of overt diabetes in patients with Stage 2 T1D has been a promising avenue of research. The FDA approved Tzield (teplizumab), an anti-CD3 antibody, to delay the onset of Stage 3 T1D in adults and pediatric patients 8 years of age and older with Stage 2 T1D. Tzield is the first and only FDA-approved pharmacologic therapy for delaying the onset of clinical diabetes and continues to be investigated for the treatment of newly diagnosed type 1 diabetics. The 2025 ADA Standards of Medical Care recommends that Tzield, to delay the onset of symptomatic T1D (stage 3), should be considered in selected individuals 8 years of age and older with stage 2 T1D, and management should be in a specialized setting with appropriately trained personnel.

- According to the prescribing information, eligibility for treatment requires that the patient's clinical history does not suggest type 2 diabetes (T2D) and that Stage 2 T1D be confirmed by documentation of the following:

- At least 2 positive pancreatic islet cell autoantibodies.

- Dysglycemia without overt hyperglycemia using an OGTT. If an OGTT is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate.

- Alternative methods for diagnosing dysglycemia does not suggest a specific or defined test, but rather alternative means of establishing the blood glucose levels indicative of dysglycemia. This could be accomplished with a fasting blood glucose draw, any blood draw measuring glucose with levels over 200 mg/dL, or blood sugar levels in response to a mixed meal prep or an alternative to the Glucola used in the OGTT at 2 hours.

- Tzield was evaluated in the pivotal Phase II, randomized, double-blind, placebo-controlled "At-Risk" TN-10 trial in patients 8 to 49 years of age who had a direct relative with T1D and were considered high risk for development of clinical diabetes (n=76).

- All patients were classified as having Stage 2 T1D defined by both of the following:

- The presence of two or more diabetes-related pancreatic islet autoantibodies (GAD65, IAA, IA-2A, ZnT8A, or ICA)

- Evidence of dysglycemia on OGTT, defined as any of the following occurring at least once (patients < 18 years) or on two occasions (patients > 18 years):

- Fasting blood glucose level of 110mg/dL to < 126 mg/dL, OR
- 2-hour postprandial glucose > 140 mg/dL and < 200 mg/dL, OR
- Postprandial glucose level at 30, 60, or 90 minutes ≥ 200 mg/dL

- Eligible patients with a first-degree relative (parent, sibling, offspring) were required to be between 8 and 45 years old, while those with a second- or third-degree relative (niece, nephew, aunt, uncle, cousin, grandchild) were between 8 and 20 years old.

- The primary endpoint of Study TN-10 was the elapsed time from randomization to development of Stage 3 T1D diagnosis.

- Stage 3 T1D was diagnosed in 20 (45%) of the Tzield-treated patients and in 23 (72%) of the placebo-treated patients. The median time from randomization to Stage 3 T1D diagnosis was 50 months for the Tzield arm and 25 months for the placebo arm. This represents a statistically significant delay in the development of Stage 3 T1D by about 2 years (p=0.0066).

- A published follow-up of the TN-10 trial reported that those in the Tzield arm had a median time to diagnosis of 59.6 months compared to 27.1 months for those in the placebo arm (p=0.01), extending the median delay in diagnosis of Stage 3 T1D with Tzield to 2.7 years. Note that this data was not reviewed by the FDA in the approval of Tzield.

- Tzield is administered intravenously once daily for 14 consecutive days. Based on the available literature, additional Tzield treatments are not recommended to delay the onset of clinical T1D in at-risk individuals.

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Policy History		
#	Date	Change Description
1.4	Effective Date: 02/12/2026	Annual review of criteria performed, no changes were made
1.3	Effective Date: 02/13/2025	Changed the fasting plasma glucose criteria requirement from 110 mg/dL to 100 mg/dL and postprandial glucose from > 200 mg/dL to ≥ 200 mg/dL to align with ADA Standards of Care (2025)
1.2	Effective Date: 02/08/2024	Annual review of criteria performed, no changes were made
1.1	Effective Date: 02/02/2023	New policy - this criteria replaces previously approved preliminary criteria
1.0	Effective Date: 01/01/2023	New Policy

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Ultomiris® (ravulizumab)
HCPCS: J1303

Background Information:

- Ultomiris is a complement inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy, generalized myasthenia gravis in those who are anti-AChR antibody-positive, and neuromyelitis optica spectrum disorder (NMOSD) in adults who are anti-aquaporin-4 (AQP4) antibody positive. Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). The subcutaneous formulation is not indicated for use in MG.

- Paroxysmal nocturnal hemoglobinuria

- Paroxysmal nocturnal hemoglobinuria is a rare acquired hematopoietic stem cell disorder in which red blood cells undergo cell lysis prematurely mediated by the alternative pathway of complement (APC). PNH arises due to a somatic mutation of a the PIGA gene whose protein product is a glycosyl transferase. Glycosyl transferase is part of the biosynthetic pathway that generates glycosyl phosphastidylinositol (GPI) that serves as an anchor for membrane bound proteins on hematopoietic lineage cells. The mutation in PIGA results in a lack of glycosyl transferase activity and near-complete or complete absence of expression of all proteins that are GPI-anchored including the complement inhibitory proteins CD55 and CD59. The deficiency of CD55 and CD59 cause the complement-mediated intravascular hemolysis characteristic of PNH.

- Phenotypic mosaicism of the peripheral blood is a characteristic feature of PNH and is based on quantitative differences in complement sensitivity. Cell complement sensitivity is divided into 3 types. PNH type I cells are defined by having normal sensitivity to complement-mediated lysis. PNH type II cells are moderately complement sensitive or 2 - 4 times more sensitive than normal. Finally, PNH type III cells are markedly complement sensitive or 15 - 25 times more sensitive than normal. Complement sensitivity varies greatly from patient to patient depending on their unique phenotypic mosaicism. Erythrocyte phenotype is clinically relevant as patients with primarily type II cells have a relatively benign clinical course. In contrast, those who have more type III cells, which are completely deficient in CD55 and CD59, will have a more severe clinical course due to increased complement-mediated hemolysis. As Ultomiris is a complement inhibitor, it was studied only in patients with greater than 5% PNH type III cells on flow cytometry.

- For patients with high disease activity, PNH complications increase significantly. High disease activity is defined as an elevated LDH greater than or equal to 1.5 times the upper limit of normal with constitutional symptoms of weakness, fatigue, hemoglobinuria, abdominal pain, dyspnea, hemoglobin less than 10 g/dL, dysphagia, and erectile dysfunction. Patients with an elevated LDH and at least one additional symptoms should begin treatment with Ultomiris.

- Thrombolytic complications are the leading cause of morbidity and mortality in PNH. Acute thrombotic events require anticoagulation with heparin. If there is no contraindication, anticoagulation should continue indefinitely for a patient with PNH who has experienced a thromboembolic complication. For patients being treated with Ultomiris and no history of thromboembolic complications, prophylactic anticoagulation may be unnecessary, although it is recommended that anticoagulation continue for those patients who experienced a thromboembolic event prior to initiating therapy with Ultomiris.

- Ultomiris has been shown to decrease the number of blood transfusions required by patients and stabilize hemoglobin levels and to be non-inferior to Soliris in regards to these endpoints. Soliris has been studied in patients receiving as few on 1 blood transfusion in 24 months while the Ultomiris studies had patients averaging at least 1 blood transfusion within the 12 months prior to the trial.

- Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat PNH, such as, Soliris.

- Atypical hemolytic uremic syndrome

- Atypical hemolytic uremic syndrome is an extremely rare disease characterized by hemolytic anemia, thrombocytopenia, and acute kidney failure. Acute presentation may also include neurological findings, including seizures, gastrointestinal symptoms, and cardiovascular involvement, including hypertensive emergency and acute coronory events. Chronic kidney disease (CKD) is the most common long-term complication and may result in the need for dialysis. The signs and symptoms of aHUS result from the formation of microthrombi in various small blood vessels of the body. These clots reduce or prevent proper blood flow to various organs especially the kidneys. Multiple factors, including certain genetic, environmental, and immunologic factors, all play a role in its development.

- The nomenclature and terminology surrounding aHUS can be confusing. Atypical hemolytic uremic syndrome is considered a form of thrombotic microangiopathy (TMA). TMA is broken down into two main forms, thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS).

- TTP is group of syndromes in which patients usually present with thrombocytopenia and microangiopathic hemolytic anemia. Despite similarities in clinical features, the underlying mechanisms of aHUS and TTP differ, altering the manner in which patients respond to different therapies. TTP results from mutations in the gene encoding a disintegrin and metalloprotease with thrombospondin type 1 motif 13 or ADAMTS13. Patients who are severely ADAMTS13 deficient, defined as ADAMTS13 activity less than 10%, have a confirmed diagnosis of TTP and may not respond to complement-inhibitor therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of TTP and therefore, Ultomiris should not be prescribed.

- HUS is also broken down into two main forms, aHUS and secondary HUS. Secondary HUS are caused by Shiga toxin E. coli, S. pneumoniae, malignancy, HIV infection, solid organ transplants, hematopoietic stem cell transplants, autoimmune disorders and the use of certain drugs or medications. HUS caused by infectious bacteria typically presents with diarrhea and responds well to antibiotic therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of infectious HUS and Ultomiris should not be initiated in these patients. Atypical hemolytic uremic syndrome typically results from complement abnormalities, however, it is a diagnosis of exclusion, meaning the diagnosis is made by excluding other primary thrombotic microangiopathy (TMA) syndromes, such as TTP or infectious HUS.

- Most patients with aHUS present with the complete triad symptoms: hemoglobin less than 10 g/dL, platelets less than 150,000/mm^3, and renal insufficiency with increased serum creatinine or the need for dialysis. The presence of schizocytes, undetectable haptoglobin, and high LDH levels confirm the microangiopathic intravascular origin of hemolysis. Ultomiris should be initiated in patients with these symptoms and a lack of secondary or infectious causes.

- Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat aHUS, such as, Soliris.

- Myasthenia gravis

- Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Approximately 10-15% of MG cases will become refractory resulting in profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Refractory disease is defined by the 2016 international consensus guidance for management of myasthenia gravis as worsening or unchanged disease despite use of corticosteroids and at least two different immunosuppressive therapies used in adequate doses for an adequate duration with persistent symptoms and/or side-effects that limit function.

- Ultomiris has only been studied and shown to be safe or effective in patients with anti-AChR antibodies. An immunologic assay to detect for the presence of anti-AChR antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has anti-AChR antibodies, at least one other confirmatory test including a positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) should be conducted.

- The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2020 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a

meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery. Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Ultomiris has not been studied in patients who have undergone thymectomy within 12 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Ultomiris in these patient populations at this time.

- Standard therapies recommended by the 2020 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, IVIG, and PLEX.

- Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.

- Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect and doses should be maintained for six months to two years of therapy and then tapered to the lowest effect dose.

- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.

- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX.

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. A number of case reports and case series support the efficacy of rituximab in patients with refractory MG. In a prospective study of 22 patients with refractory MG treated with rituximab, the mean time to relapse was 17 months. Among 14 patients taking prednisone, the mean daily dose decreased from 25 mg at baseline to 7 mg after treatment with a mean follow-up of 29 months. In an observational study of 72 patients with new-onset or refractory generalized MG, those treated with low-dose rituximab had shorter time to remission, lower use of adjunctive treatments, and fewer adverse events than patients treated with conventional immunosuppressive therapy.

- Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat MG, such as, Soliris, or one medication is superior to the other.

- Neuromyelitis optica spectrum disorder

  - Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage mainly of the optic nerves and spinal cord. NMOSD is thought to be primarily mediated by the humoral immune system and the autoantibody aquaporin-4 (AQP4) which is released by B-cells and plasma blasts. Serum anti-AQP4 levels have been shown to correlate with disease activity, decrease after immunosuppressive therapy, and remain low during remissions.

  - Ultomiris is indicated for the treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-AQP4 antibody positive.

  - Safety and efficacy were established in CHAMPION-NMOSD trial, an open-label phase III study of 58 patients with NMOSD who were anti-AQP4 antibody positive, had at least 1 relapse in the last 12 months prior to study screening, and an Expanded Disability Status Scale (EDSS) score less than or equal to 7. The primary endpoint was the time to the first adjudicated on-trial relapse. No on-trial relapses were observed in Ultomiris-treated patients during the primary treatment period, representing a statistically significant difference between the Ultomiris and placebo treatment arms in time to first on-trial relapse (p-value < 0.0001). The hazard ratio (95% confidence interval [CI]) for Ultomiris compared with placebo was 0.014 (0.000, 0.103), representing a 98.6% reduction in the risk of relapse. Ultomiris-treated patients experienced similar improvement in time to first on-trial relapse with or without concomitant treatment.

  - Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat NMOSD, such as Rituxan®, Enspryng, or Uplizna.

- No American treatment guidelines are available for neuromyelitis optica spectrum disorders. The European Federation of Neurological Societies published guidelines for the diagnosis and management of neuromyelitis optica in 2010. Long-term treatment options should be initiated as soon as the diagnosis is made to prevent attacks and reduce the risk of permanent disability, but evidence from randomized-controlled trials for any particular medication is lacking. The guidelines recommend azathioprine plus prednisone or rituximab as first-line therapy to prevent attacks. If first-line treatment is ineffective or the patient develops steroid-dependence for clinical remission, alternative immunosuppressive therapies need to be considered. Second-line therapy includes cyclophosphamide, mitoxantrone, methotrexate, IVIG, mycophenolate mofetil, and intermittent plasma exchange. The guidelines have not been updated to include Uplizna, Soliris, Ultomiris, or Enspryng.

- While a variety of immunosuppressive therapy are regarded as first-line therapy based on primarily observational or single-arm data, use has fallen out of favor due to lack of efficacy. The most widely prescribed treatments include azathioprine and mycophenolate mofetil. However, if given, they are often prescribed with low doses of corticosteroids to treat the relapse and the steroids are weaned slowly.

- Rituximab targets the CD20 antigen on B-cells and leads to profound B-cell depletion, principally over an antibody-dependent cell cytotoxicity mechanism and decreases attack frequency and severity in patients with NMOSD. Most of the investigations revealed that Expanded Disability Status Score (EDSS) improved significantly in all patients with rituximab treatment after treatment with rituximab and relapse rates decreased by up to 88%. No new or enlarged lesions or pathological gadolinium enhancement was observed in serial brain and spinal cord MRIs, except for those observed concomitantly with clinical relapses and the median length of spinal cord lesions was significantly reduced after therapy. Paradoxical relapses may occur shortly after initiation of rituximab therapy so it is important to allow enough time for the rituximab to become effective. Complete suppression of CD19-positive B-lymphocytes takes one month.

- There are multiple options for the long-term treatment of NMOSD. There an no clinical trials comparing the efficacy of one therapy to another. Choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability.

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Policy History		
#	Date	Change Description
1.6	Effective Date: 06/05/2025	Annual review – no changes to criteria at this time
1.5	Effective Date: 06/06/2024	Updated to include new indication of neuromyelitis optica spectrum disorder and add a step through Empaveli for the PNH indication
1.4	Effective Date: 10/12/2023	Annual review – no changes to criteria at this time
1.3	Effective Date: 10/06/2022	Updated to include the new subcutaneous formulation
1.2	Effective Date: 06/09/2022	Updated to include new indication of myasthenia gravis and remove prescriber requirements
1.1	Effective Date: 06/10/2021	Update to remove platelet requirement for PNH and the percentage of PNH type III cells required
1.0	Effective Date: 01/01/2021	New Policy

Uplizna™ (inebilizumab)
HCPCS: J1823

Background Information:

- Neuromyelitis optica spectrum disorders (NMOSD)

  - Neuromyelitis optica spectrum disorders are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage mainly of the optic nerves and spinal cord. NMOSD is thought to be primarily mediated by the humoral immune system and the autoantibody aquaporin-4 (AQP4) which is released by B-cells and plasma blasts. Serum anti-AQP4 levels have been shown to correlate with disease activity, decrease after immunosuppressive therapy, and remain low during remissions.

  - Uplizna is indicated for the treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-AQP4 antibody positive. Uplizna should be started with a loading dose of 300 mg at weeks 0 and 2 followed by 300 mg every 6 months starting from the first infusion thereafter.

  - Safety and efficacy were established in the multicenter, double-blind, randomized placebo-controlled, phase 2/3 N-Momentum study of 230 patients with NMOSD. In the trial, 213 of the 230 patients were anti-AQP4 antibody positive. Patients were included if they had a history of at least one attack requiring rescue therapy in the prior year and had an Expanded Disability Status Scale score of less than or equal to 7.5. Patients were randomized to receive 300 mg of Uplizna on day 1 and 15 followed by every 6 months thereafter or placebo in a 3:1 ratio. The primary endpoint was the time to the onset of the first adjudicated relapse on or before day 197. The risk of an NMOSD relapse in the 161 anti-AQP4 antibody positive patients who were treated with Uplizna was reduced by 77% when compared to the placebo treatment group ($p < 0.0001$). There was no evidence of a benefit in patients who were anti-AQP4 antibody negative.

  - Uplizna has not been studied and there is no data to support use in combination with other medications used to treat NMOSD, such as Rituxan®, Enspryng, or Soliris.

  - No American treatment guidelines are available for neuromyelitis optica spectrum disorders. The European Federation of Neurological Societies published guidelines for the diagnosis and management of neuromyelitis optica in 2010. Long-term treatment options should be initiated as soon as the diagnosis is made to prevent attacks and reduce the risk of permanent disability, but evidence from randomized-controlled trials for any particular medication is lacking. The guidelines recommend azathioprine plus prednisone or rituximab as first-line therapy to prevent attacks. If first-line treatment is ineffective or the patient develops steroid-dependence for clinical remission, alternative immunosuppressive therapies need to be considered. Second-line therapy includes cyclophosphamide, mitoxantrone, methotrexate, IVIG, mycophenolate mofetil, and intermittent plasma exchange. The guidelines have not been updated to include Uplizna, Soliris, or Enspryng.

- While a variety of immunosuppressive therapies are regarded as first-line therapy based on primarily observational or single-arm data, use has fallen out of favor due to lack of efficacy. The most widely prescribed treatments include azathioprine and mycophenolate mofetil. However, if given, they are often prescribed with low doses of corticosteroids to treat the relapse and the steroids are weaned slowly.

- Rituximab targets the CD20 antigen on B-cells and leads to profound B-cell depletion, principally over an antibody-dependent cell cytotoxicity mechanism and decreases attack frequency and severity in patients with NMOSD. Most of the investigations revealed that Expanded Disability Status Score (EDSS) improved significantly in all patients with rituximab treatment after treatment with rituximab and relapse rates decreased by up to 88%. No new or enlarged lesions or pathological gadolinium enhancement was observed in serial brain and spinal cord MRIs, except for those observed concomitantly with clinical relapses and the median length of spinal cord lesions was significantly reduced after therapy. Paradoxical relapses may occur shortly after initiation of rituximab therapy so it is important to allow enough time for the rituximab to become effective. Complete suppression of CD19-positive B-lymphocytes takes one month.

- There are multiple options for the long-term treatment of NMOSD. There an no clinical trials comparing the efficacy of one therapy to another. Choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability.

- IgG4 related disease (IgG4-RD)

  - IgG4-RD is a recently established systemic disease that is characteristically associated with elevated serum IgG4 levels and believed to be caused by autoimmune mechanisms. The clinical features of IgG4-RD include systemic distribution; imaging findings of swelling, nodules, and/or wall thickening; high serum IgG4 levels; abundant IgG4-bearing plasma cell infiltration and fibrosis in affected organs; a favorable response to corticosteroid therapy; and coexistence with other IgG4-RD manifestations simultaneously or in a metachronous fashion. The systemic distribution of IgG4-RD seems to be capable of affecting every organ causing issues including autoimmune pancreatitis, Mikulicz's disease, respiratory disease, sclerosing cholangitis, kidney disease, and retroperitoneal fibrosis.

  - High serum IgG4 levels and increased IgG4-bearing plasma cell infiltration in affected organs are the most important characteristic features of IgG4-RD and the major indicators in the diagnostic process. However, because these findings are similar for other inflammatory or malignant conditions, their presence does not necessarily exclude other disorders. In addition, while other clinical, serologic, radiologic, and pathologic features all contribute to the classification of IgG4-RD, none of these approaches alone provides definitive evidence for the diagnosis of patients. Therefore, in 2019, the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) developed an international set of classification criteria for IgG4-RD. The 3 step classification process includes demonstration that a potential IgG4-RD case has involvement of at least 1 of 11 possible organs in a manner consistent with IgG4-RD; exclusion criteria consisting of a total of 32 clinical, serologic, radiologic, and pathologic items that if present eliminates the patient from IgG4-RD classification; and 8 weighted inclusion criteria domains addressing clinical findings, serologic results, radiology assessments, and pathology interpretations. A score on the classification system of greater than or equal to 20 correlates to an IgG4-RD diagnosis with a specificity of 99.2% (95% CI: 97.2%, 99.8%) and a sensitivity of 85.5% (95% CI: 81.9%, 88.5%).

- The 2015 International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease recommend treatment with 30 – 40 mg/day of prednisone as first-line treatment for remission induction in all patients with active, untreated IgG4-RD. Typically the initial glucocorticoid dose should be maintained for 2 – 4 weeks after which it can be tapered gradually. The goal of induction therapy for many patients is to discontinue glucocorticoid use 3 – 6 months after the start of treatment, however, many clinicians recommend the use of low-dose glucocorticoid maintenance therapy for up to 3 years. Retreatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction.

- Following a successful course of induction therapy for certain high-risk patients or after a relapse, patients can benefit from maintenance therapy. The introduction of a steroid-sparing agent, such as, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclophosphamide, or rituximab for continuation in the remission maintenance period can be considered. Patients with multiorgan disease, significantly elevated serum IgG4 concentrations, involvement of the proximal bile ducts, and a history of disease relapse are at higher risk of early recurrence following remission induction and can benefit from addition of steroid sparing agents from the start of glucocorticoid inducation. Patients with organ-threatening IgG4-RD manifestations and those with an elevated risk of relapse will also likely benefit from maintenance therapy in an effort to minimize morbidity.

- Myasthenia gravis

  - Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Approximately 10-15% of MG cases will become refractory resulting in profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Refractory disease is defined by the 2016 international consensus guidance for management of myasthenia gravis as worsening or unchanged disease despite use of corticosteroids and at least two different immunosuppressive therapies used in adequate doses for an adequate duration with persistent symptoms and/or side-effects that limit function.

  - Uplizna is only indicated for use in patients with anti-AChR or anti-MuSK antibodies. An immunologic assay to detect for the presence of anti-AChR and anti-MuSK antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has one of these antibody types, at least one other confirmatory test should be conducted. A positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) all can be used to verify anti-AChR MG. Only a repetitive nerve stimulation (RNS) or single-fiber electromyography (SFEMG) can be used to confirm anti-MuSK antibody positive disease.

  - The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2021 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on class II evidence from a meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery.

Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Uplizna has not been studied in patients who have undergone thymectomy within 12 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Uplizna in these patient populations at this time.

- Standard therapies recommended by the 2021 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, IVIG, and PLEX.
  - Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.
  - Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.
  - Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect and doses should be maintained for six months to two years of therapy and then tapered to the lowest effect dose.
  - Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.
  - PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX.
  - There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. A number of case reports and case series support the efficacy of rituximab in patients with refractory MG. In a prospective study of 22 patients with refractory MG treated with rituximab, the mean time to relapse was 17 months. Among 14

patients taking prednisone, the mean daily dose decreased from 25 mg at baseline to 7 mg after treatment with a mean follow-up of 29 months. In an observational study of 72 patients with new-onset or refractory generalized MG, those treated with low-dose rituximab had shorter time to remission, lower use of adjunctive treatments, and fewer adverse events than patients treated with conventional immunosuppressive therapy.

- Uplizna has not been studied and there is no data to support use in combination with other medications used to treat MG, such as, Soliris, or one medication is superior to the other.

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Policy History		
#	Date	Change Description
1.7	Effective Date: 02/12/2026	Updated to include the new indication for use in myasthenia gravis
1.6	Effective Date: 06/05/2025	Updated to include the new indication for use in IgG4 related disease
1.5	Effective Date: 04/10/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 04/06/2023	Updated to remove the step through Rituxan or a rituximab biosimilar
1.2	Effective Date: 12/01/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 12/09/2021	Annual review of criteria was performed, no changes were made

Ustekinumab Products
Imuldosa™ (ustekinumab-srlf) Q5098
Otulfi™ (ustekinumab-aauz) Q9999
Pyzchiva® (ustekinumab-ttwe) Q9997
Selarsdi™ (ustekinumab-aekn) Q9998
Starjemza (ustekinumab-hmny) J3590
Stelara® (ustekinumab) J3358
Steqeyma® (ustekinumab-stba) Q5099
Ustekinumab J3590
Ustekinumab-aauz J3590
Ustekinumab-aekn J3590
Ustekinumab-auub Q5138
Ustekinumab-srif Q5098
Ustekinumab-stba Q5099
Ustekinumab-ttwe J3590
Wezlana™ (ustekinumab-auub) Q5138
Yesintek™ (ustekinumab-kfce) Q5100

Background Information:

- Ustekinumab is an interleukin (IL)-12 and IL-23 inhibitor available as the innovator product Stelara and its biosimilars Imuldosa, Otulfi, Pyzchiva, Selarsdi, Starjemza, Steqeyma, Wezlana, and Yesintek. Wezlana was also granted interchangeability status by the FDA, while the FDA provisionally determined that Pyzchiva would be interchangeable with Stelara as it is currently subject to an unexpired period of exclusivity for the first interchangeable biosimilar biological products.

- Stelara and its biosimilars are approved for the treatment of psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. They may be administered as a subcutaneous (SC) injection or via intravenous (IV) infusion. Administration via IV infusion is reserved for induction therapy in Crohn's disease and ulcerative colitis utilizing a single weight-based dose. After induction, the transition is made to subcutaneous dosing for maintenance therapy.

- Use of ustekinumab in combination with other biologic agents or targeted immunosuppressants has not been sufficiently evaluated for safety and efficacy and therefore is not recommended.

- Crohn's Disease

- The 2018 American College of Gastroenterology (ACG) guidelines establish therapeutic recommendations for patients with CD based upon disease location, disease severity, disease-associated complications, and future disease prognosis. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Current therapeutic approaches should be considered a sequential continuum to treat acute disease or induce clinical remission and then to maintain response/remission. In general, clinical evidence of improvement should be evident within 2 – 4 weeks and the maximal improvement should occur within 12 – 16 weeks. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease, have their medication dose adjusted in order to attempt to optimize therapy, or advance to treatment for moderate to severe disease according to their clinical status.

- Corticosteroids are used primarily for the treatment of flares of CD. Conventional corticosteroids are effective for reducing the signs and symptoms of active CD and induction of remission in patients with moderately to severely active CD. Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active disease. The ACG guidelines recommend prednisone equivalent doses ranging from 40 to 60 mg per day. These doses are typically maintained for 1 –2 weeks and tapered at 5 mg weekly until 20 mg and then 2.5 –5 mg weekly. Once begun, care should be taken to ensure that corticosteroids are successfully discontinued, and steroid-sparing agents should be used.

- In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, mercaptopurine, azathioprine, and intramuscular or subcutaneous methotrexate are effective steroid-sparing agents and guideline recommended. Maximum effectiveness of these agents can be seen between 8 to 12 weeks from therapy initiation. Methotrexate is also recommended in combination with steroids as effective for treatment of moderately active steroid-dependent/resistant CD. Cyclosporine, tacrolimus, and mycophenolate are not recommended for treatment of CD.

- Biologics, such as TNFi are recommended to treat CD that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. The ACG guidelines also recommend the use of biologics in combination with immunosuppressants to help decrease the formation of antibodies against the biologic therapy. There are no robust, published studies to support use of biologic agents in combination.

- Ustekinumab is recommended in patients with moderate to severe CD who have had prior treatment failures with corticosteroids, thiopurines, methotrexate, or TNFi.

- The 2021 American Gastroenterological Association (AGA) guidelines include similar recommendations for the management of moderate-to-severe CD compared to the recommendations cited in the 2018 ACG guidelines. Both guidelines recommend corticosteroids over no treatment for induction of remission. Additionally, both guidelines recommend thiopurines, such as azathioprine or 6-mercaptopurine, as

steroid-sparing agents for maintenance of remission. The AGA guidelines also recommend the same biologic agents cited in the ACG guidelines for treatment of CD, with the exception of Tysabri® (natalizumab), which the ACG suggests against use of due to its associated risk of progressive multifocal leukoencephalopathy (PML).

- Of note, the AGA guidelines conditionally recommend earlier introduction of biologic therapy prior to failure of corticosteroids; however, this recommendation is supported by a low level of clinical evidence. To date, no blinded randomized controlled trials (RCTs) have demonstrated the superiority of early introduction of biologic therapy compared to conventional induction therapy with corticosteroids followed by steroid-sparing therapy. The 2021 AGA guideline authors also acknowledge that earlier therapy with either combination immunomodulator plus biologic therapy or biologic monotherapy may result in over-treating some patients and potentially exposing them to treatment-related risks and costs with limited benefit.

- Ulcerative Colitis

  - The 2019 ACG guidelines and the 2020 AGA guidelines for ulcerative colitis (UC) state therapeutic management in UC should be guided by the specific diagnosis, an assessment of disease activity, and disease prognosis. Treatment selection should be based not only on inflammatory activity but also on disease prognosis.

  - Remission can be induced using a variety of medications, including, oral 5-aminosalicylates (5-ASA), corticosteroids, or biologic agents. In patients with mild to moderately active disease, treatment with 5-ASA therapy has proven to be safe and efficacious for induction. Recommended dosing is 2 grams per day of oral 5-ASA or at least 1 gram per day of rectal 5-ASA with improvement usually seen within 4 weeks. A typical treatment course may be up to 8 weeks.

  - Oral steroids are recommended for induction for patients with severe disease or those who did not respond to 5-ASA therapy. The typical starting doses of oral prednisone are 40 – 60 mg per day, and clinical response is expected within 5 – 7 days of treatment. A typical treatment course with oral prednisone is 14 days. The duration of systemic corticosteroids should be as short as possible with early initiation of steroid-sparing therapy. The speed of the taper should be guided by clinical symptoms, cumulative steroid exposure, and onset of action of alternate therapies. Those unable to taper off of 10-20 mg of prednisone per day without relapsing are considered steroid dependent. Use systemic corticosteroids for maintenance of remission is not recommended.

  - Thiopurines, such as azathioprine and mercaptopurine, can be used to maintain remission. Guidelines recommend use of thiopurines over no medication or corticosteroids for maintenance therapy. Thiopurines are slow acting with maximum effectiveness of these agents being seen between 8 to 12 weeks from therapy initiation. They do not induce remission in moderately to severely active ulcerative colitis. Similarly, methotrexate is not an effective induction agent for induction or maintenance of remission.

- In patients with moderate to severe disease, TNFi, Entyvio® (vedolizumab), and ustekinumab are recommended for the induction and maintenance of remission. For patients with moderate to severe disease in remission, guidelines do not recommend biologic monotherapy over thiopurine monotherapy. Thiopurines can be used as adjunctive therapy for reducing immunogenicity against biologic therapy and are guideline recommended.

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12. Skyrizi (risankizumab-rzaa) [prescribing information]. North Chicago, IL: AbbVie Inc; May 2023.
13. Wezlana [prescribing information]. Thousand Oaks, CA: Amgen; October 2023.
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15. Selardsi [prescribing information]. Leesburg, VA: Alvotech USA Inc; April 2024.
16. Otulfi [prescribing information]. Lake Zurich, IL: Fresenius Kabi; September 2024.
17. Imuldosa [prescribing information]. Raleigh, NC: Accord BioPharma Inc; October 2024.

18. Yesintek [prescribing information]. Cambridge, MA: Biocon Biologics, Inc; November 2024.
19. Steqeyma [prescribing information]. Jersey City, NJ: Celltrion USA, Inc.; December 2024.
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Policy History		
#	Date	Change Description
1.6	Effective Date: 02/12/2026	Updated policy to include biosimilars ustekinumab-srlf and ustekinumab-stba
1.5	Effective Date: 12/04/2025	Updated policy to include biosimilar ustekinumab-auub
1.4	Effective Date: 08/07/2025	Updated policy to include biosimilar Starjemza
1.3	Effective Date: 06/05/2025	Updated policy to include biosimilars: ustekinumab, ustekinumab-aauz, ustekinumab-aekn, and ustekinumab-ttwe
1.2	Effective Date: 02/13/2025	Updated policy to include biosimilars Steqeyma and Yesintek
1.1	Effective Date: 12/12/2024	Updated include Otulfi and Imuldosa
1.0	Effective Date: 11/03/2024	New Policy

Vabysmo™ (faricimab-svoa)
HCPCS: J2777

Background Information:

- Intravitreal injections of anti-vascular endothelial growth factor (VEGF) have been widely used by ophthalmologists to treat a variety of ocular diseases. They are injected directly into the eye to prevent the formation of new blood vessels and reduce blood vessel leakage and inflammation. Vabysmo is an anti-VEGF therapy indicted for neovascular (wet) age related macular degeneration (AMD), diabetic macular edema (DME), and macular edema following retinal vein occlusion (RVO).

- Age-related Macular Degeneration

- Age-related macular degeneration is a degenerative disease of the macula that results primarily in loss of central vision. Wet AMD is characterized by growth of abnormal vessels into the subretinal space. These abnormal blood vessels leak leading to collections of subretinal fluid and/or blood beneath the retina. The 2022 American Academy of Ophthalmologists (AAO) Age-Related Macular Degeneration Preferred Practice Pattern Guidelines recommend observation and early detection, antioxidant vitamin and mineral supplements, and intravitreal injections of anti-VEGF agents for the management of wet AMD. Guidelines recommend Eylea™, Avastin®, Vabysmo, or Lucentis® for treatment. The guidelines have not been updated with Beovu®, Byooviz™, and Susvimo™.

- Diabetic Macular Edema

- Diabetic retinopathy and DME are common complications and the ocular manifestations of end-organ damage in diabetes mellitus. The 2025 AAO Diabetic Retinopathy Preferred Practice Pattern Guidelines state the goals of therapy for DR and DME include improvement or stabilization of visual function, improvement in vision-related quality of life, and optimal control of blood glucose, blood pressure, and other metabolic risk factors. Patients should always be treated with anti-VEGF therapy if they have severe non-proliferative DR or proliferative DR with center-involved macular edema. In cases of mild to moderate non-proliferative DR with center-involved macular edema, patients should also receive intravitreal injections. The guidelines support the use of Lucentis, Eylea, Vabysmo, and Avastin. AAO recommendations were based on trials comparing Eylea, Avastin, and Lucentis to focal laser treatment. All trials showed that treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years compared to laser treatment.

- Retinal Vein Occlusion

- Retinal vein occlusion occurs when there is partial or complete obstruction of a retinal vein. Vision loss can occur with RVO and is associated with macular ischemia or edema, retinal hemorrhages, vitreous hemorrhage, or epiretinal membrane formation. The 2025 AAO Retinal Vein

Occlusions Preferred Practice Pattern Guidelines recommend anti-VEGF therapy as first-line treatment for macular edema caused by RVO. The guidelines support the use of Lucentis, Eylea, and Avastin. The guidelines state VEGF inhibitors, Eylea, Avastin, and Lucentis, are more effective than sham injection or laser therapy in maintaining or improving visual acuity in patients with macular edema secondary to RVO.

- There are very few randomized control trials that assess the efficacy of one anti-VEGF therapy over another. Of the two that are available, Avastin, Eylea, and Lucentis were all shown to be non-inferior to each other, and because of this, choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability. However, a 2015 study conducted by Wells, et al. did show Eylea was superior to Avastin therapy when patients had a visual acuity of less than or equal to 20/50. In addition, a subcohort analysis of the YOSEMITE AND RHINE trials showed Vabysmo demonstrated BCVA gains similar to aflibercept, while demonstrating numerically greater improvements in anatomic outcomes at years 1 and 2. Therefore, in these scenarios Avastin should not be used prior to Eylea or Vabysmo.

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Policy History		
#	Date	Change Description
1.3	Effective Date: 06/05/2025	Annual review of criteria was performed, no changes were made
1.2	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 06/08/2023	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 05/01/2023	New Policy

Veopoz™ (pozelimab-bbfg)
HCPCS: J9376

Background Information:

- Complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) disease is an ultra-rare, potentially fatal, inherited autoimmune disorder. It is caused by a lack of CD55 protein and the inability to control complement activity. This leads to damaged blood and lymph vessels in the lower GI tract and a loss of protective immune proteins and blood cells. Patients experience abdominal pain, bloody diarrhea, nausea, vomiting, malabsorption, edema, delayed growth, recurrent lung infections, and blood clots.

- Diagnosis of CHAPLE disease is made based on a combination of factors. Patients will exhibit a clinical history of protein-losing enteropathy (PLE) symptoms, such as hypoalbuminemia and hypogammaglobulinemia. Genetic testing must be performed to confirm a biallelic CD55 loss-of-function mutation on the CD55 gene. Furthermore, patients with CHAPLE disease will have extensive lymphangiectasia upon histological assessment of intestinal biopsy samples or resections.

- Supportive care had been the mainstay of treatment and includes anticoagulation therapy, a low-fat medium-chain triglyceride–supplemented diet, supplementation of iron, fat-soluble vitamins, and minerals, use of immunoglobulin replacement therapy for recurrent infections, and albumin infusions. In recent years, Soliris, a C5 complement inhibitor, has been studied and used for CHAPLE disease. It is now considered the treatment of choice due to the results from a clinical trial of 3 patients with CHAPLE disease showing marked clinical improvement with resolution of gastrointestinal symptoms, improved overall well-being, growth, and quality of life, and increases in albumin and total protein levels. In correlation with the clinical improvements, progress was observed in all laboratory outcome parameters including increases in albumin and total protein levels and up to an 80% reduction in membrane attack complex deposition on leukocytes (p-value < 0.001). The progress persisted over 18 months of treatment without any severe adverse events.

- Veopoz is another C5 complement inhibitor indicated for the treatment of adult and pediatric patients 1 year of age and older with CHAPLE disease.

- Safety and efficacy were evaluated in a single-arm study in which patients' outcomes were compared to pre-treatment data in patients with active CHAPLE disease. Patients' diagnoses were based on a clinical history of PLE symptoms and with a confirmed genotype of biallelic CD55 loss-of-function mutation. Active disease was defined as a serum albumin concentration of less than or equal to 3.2 g/dL with one or more of the following signs or symptoms within the last six months: diarrhea, abdominal pain, peripheral edema, or facial edema. Patients received a single 30 mg/kg loading dose of Veopoz administered by intravenous infusion followed by a weekly maintenance subcutaneous injection starting one week after the loading dose. Ten patients ranging from 3 to 19 years of age were assessed for efficacy. All 10 patients achieved a serum albumin concentration of at least 3.5 g/dL by week 12 which was maintained through at least 72 weeks. All 10 patients

also demonstrated a reduction in the number of hospitalizations and number of albumin transfusions over the first 48 weeks of treatment as compared to the 48 weeks prior to treatment.

- Veopoz has not been studied and there is no data to support use in combination with other medications used to treat CHAPLE disease, such as, Soliris.

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Policy History		
#	Date	Change Description
1.2	Effective Date: 10/09/2025	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 10/03/2024	Annual review – no changes to the criteria at this time
1.0	Effective Date: 10/15/2023	New Policy

Vyjuvek™ (beremagene geperpavec-svdt)
HCPCS: J3401

Background Information:

- Epidermolysis bullosa, or EB, is a rare, inherited connective tissue disorder that causes abnormalities in cohesion of layers of the skin. There are 4 different types of EB, one of which is dystrophic epidermolysis bullosa (DEB) which makes up about 25% of EB cases. DEB can be inherited dominantly or recessively, with recessive cases being the most common and most severe. Patients with dominant DEB have few complications and survive into adulthood, while those with recessive only live to their 3rd or 4th decade, often dying of squamous cell carcinoma or renal failure.

- DEB is caused by mutations in the *COL7A1* gene which codes for Type 7 collagen, whose responsibility is to bind the dermis to the epidermis. In DEB, Type 7 collagen is either reduced or completely absent, creating extremely fragile skin that blisters between the dermis and the epidermis and tears from even the most minor friction or trauma, such as holding a pencil or putting on a shirt. The constant cycle of blistering, wounding, and re-healing that occurs with DEB contributes to complications like infection, debilitating scarring, physical deformities, pubertal or growth delay, anemia, esophageal blistering, spinal fractures, and squamous-cell carcinoma.

- Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa developed on behalf of the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International (2020) recommend every patient with an established or suspected diagnosis of EB undergo genetic testing (level of evidence 2++, grade of recommendation B). Skin biopsy of an induced blister with immunofluorescence mapping (IFM) and/or transmission electron microscopy (TEM) may also be useful in the diagnosis of EB; however, with DEB, particularly in mild cases, the results of these tests may not deliver a useful result and genetic testing documenting the presence of mutations in the *COL7A1* gene would be required to deliver the final diagnosis.

- The goal of treatment is to promote wound healing, prevent infection and other complications, and protect the skin. Prior to the FDA approval of DEB therapies, there were no approved treatments for any form of EB. Management has historically been supportive, involving a multidisciplinary team that includes wound care, infection and pain control, nutritional support, and prevention and treatment of complications.

- A consensus statement from the European Reference Network for Rare Skin Diseases on the practical management of EB (2021) and an international consensus on best practice guidelines for skin and wound care in EB from Wounds International (2017) regard wound care as the cornerstone of treatment for EB patients. Skin and wound assessments should be undertaken regularly and management tailored to suit both the type of EB and the specific characteristics of the wound, as well as the needs and preferences of the patient. Regular follow up on patient

and caregiver adherence to treatment should also be performed with adaptation of the care plan to meet the patient's needs and preferences, as needed.

- Malnutrition, anemia, pruritis, and pain can compromise a patient's ability to heal; therefore, these conditions should be treated appropriately to optimize long-term wound healing and minimize further skin damage and trauma.

- Atraumatic dressings should be utilized to prevent blistering and skin and wound bed damage. Dressing examples include polymeric membrane, super-absorbent, soft silicone mesh or foam, lipido-colloid, foam, and keratin. Most dressings should be changed every 1 to 3 days unless otherwise noted by the manufacturer or required by the patient's individual needs.

- Preventative measures to avoid and/or reduce blister formation should also be enforced, such as padding trauma-exposed sites, avoidance of tight clothing, choosing suitable footwear with appropriate insoles and/or orthotics. Any intact blisters should be lanced and drained as they are not self-limiting.

- Wound management in DEB must also address infection, critical colonization, and protection from additional trauma. Bacterial burden can be controlled by systemic or topical therapies.

- Healing rate of wounds should be monitored by checking advancement of the wound edges. A reduction of 20-40% in 2 to 4 weeks may predict healing by 12 weeks. Pain and itch reduction and resolution of infection should also be evaluated.

- Recently approved treatments for DEB include topical gene therapy Vyjuvek for the treatment of wounds in patients with DEB and mutations in the *COL7A1* gene, Filsuvez®, a topical gel that promotes general wound healing of DEB-associated wounds, and Zevaskyn™, an autologous cell sheet-based gene therapy for the treatment of wounds in adults and pediatric patients with RDEB. All three products work locally to heal open skin wounds and do not treat extracutaneous manifestations of DEB; therefore, supportive and palliative care will continue to remain essential even in patients receiving treatment with FDA-approved therapies.

- Vyjuvek was approved by the FDA for the treatment of wounds in patients 6 months of age and older with DEB with mutations in the *COL7A1* gene. It is the first FDA-approved treatment for any type of EB, and the first non-invasive, topical, and redosable gene therapy approved by the FDA. Unlike most other gene therapies, including Zevaskyn, Vyjuvek is "off the shelf", meaning therapy does not need to be made from the patient's own cells so the patient does not have to wait for the drug to be manufactured prior to initiating therapy. Because Vyjuvek works locally at the site of application, it should be used in addition to standard of care wound management and supportive/palliative care for DEB. The use of Vyjuvek has not yet been addressed by any guidelines or consensus statements.

- Vyjuvek utilizes an engineered herpes simplex virus vector virus to deliver two copies of functional *COL7A1* genes to affected cells when applied directly to the wound. Upon application, the patient's skin cells take up the genetic code housed in the vector virus and use it to produce functional COL7A1 protein. This protein assembles into anchoring fibrils, or Type 7 collagen, which holds the dermis and epidermis together to prevent and minimize blister formation between the skin layers.

- The safety and effectiveness of Vyjuvek was established primarily in the Phase III, multicenter, randomized, double-blind, placebo-controlled, intra-patient GEM-3 trial. Eligible patients were required to have a clinical diagnosis of DEB, characterized by blistering, wounds, and scarring, and confirmed by genetic testing. Patients were also required to have two cutaneous wounds similar in size, appearance, and anatomical regions. One wound from each pair was treated with Vyjuvek and the other treated with placebo. Wound sites with current evidence or history of squamous-cell carcinoma or active infection were excluded as sites for application of Vyjuvek or placebo.

- Of the 31 patients enrolled in the trial, one had a dominant DEB genotype while the remaining 30 had a recessive DEB genotype. The age of the trial population ranged from 1 year to 44 years old.

- Patients were randomized to once-weekly treatment with Vyjuvek or placebo until wound closure over a 6-month treatment period. Once a wound closed, product application was omitted, but if a healed wound reopened at any point in the study, then weekly application was resumed.

- The primary efficacy endpoint was complete wound healing at weeks 22 and 24 or weeks 24 and 26, defined as 100% wound closure from exact wound area at baseline evaluated at two consecutive visits two weeks apart. Efficacy was further supported by the secondary endpoint of complete wound healing at weeks 8 and 10 or weeks 10 and 12.

- Vyjuvek met its primary endpoint, with 65% of Vyjuvek-treated wounds achieving complete wound healing at 6 months compared to only 26% of placebo-treated wounds ($p=0.012$). Secondary endpoint was also met, with 68% of Vyjuvek-treated wounds achieving complete wound healing at weeks 8 and 10 or weeks 10 and 12 compared to 23% of placebo-treated wounds ($p=0.003$).

- Vyjuvek gel must be prepared at the pharmacy by mixing the Vyjuvek biological suspension into the excipient gel for immediate use within 8 hours of mixing, and application should only be performed by a healthcare professional. The gel should be applied to wounds until they are completely closed before selecting new wounds to treat. Should previously treated wounds re-open, their weekly treatment should be prioritized per the prescribing information.

- Additional gene and cell therapies are in development for the treatment of DEB. At present, there is no literature to support combination use of multiple gene therapies for the treatment of DEB.

- Provider portals are used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence

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Policy History		
#	Date	Change Description
1.2	P&T Date: 06/05/2025 Effective Date: 07/21/2025	Added criteria requiring provision of clinical outcome information within the appropriate provider portal

1.1	Effective Date: 06/06/2024	Added criteria requiring attestation of adherence to standard wound care measures and prevention of concomitant use with other DEB gene therapies
1.0	Effective Date: 09/01/2023	New Policy

Wainua™ (eplontersen)
HCPCS: J3490

Background Information:

- In ATTR, TTR misfolds, causing it to aggregate into amyloid fibrils that accumulate in organs, nerves, and tissues. The buildup of these amyloid deposits results in progressive dysfunction at the site of deposition. Amyloid deposition can occur in the heart, gastrointestinal tract, kidneys, thyroid, salivary glands, eyes, peripheral nervous system, and central nervous system. The phenotype is driven by deposition site and may be predominantly cardiac, neurologic, or mixed.

- There are two types of ATTR: hereditary (hATTR), or variant, which is due to inherited mutations of the TTR gene that cause misfolding of the tetramer subunits, and wild-type, which occurs in the presence of a normal TTR gene, is typically associated with aging, and is most often diagnosed in men 65 years and older. In wild-type ATTR, TTR typically only deposits in the heart and manifests as cardiac symptoms. hATTR, in contrast, may be predominantly neuropathic, cardiomyopathy, or a mixed phenotype characterized by both

- ATTR is the most common form of hereditary amyloidosis. Approximately 120 different mutations or gene deletions have been identified in the TTR gene, with Val30Met as the most prevalent in the world.

- hATTR with polyneuropathy (hATTR-PN) is the most common neurologic manifestation. Without treatment, patients will have progressive neuropathy and disability ultimately resulting in death within 10-15 years of disease onset.

- Patients with hATTR-PN may present with peripheral neuropathy (sensory and motor; tingling or increased pain in the hands, feet and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking), autonomic neuropathy (e.g., orthostasis, abnormal sweating, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety]), GI impairment, cardiomyopathy, nephropathy, or ocular deposition. Most hATTR-PN cases, however, are classified as neuropathic.

- Amyloid deposition induces a length-dependent peripheral neuropathy beginning in the lower limbs with symptoms like toe discomfort due to numbness and spontaneous pain. Continued aggregation of amyloid on the nerve fibers contributes to sensory loss extending upwards toward the proximal lower limbs as motor deficits and impaired sensations occur. Walking becomes increasingly difficult as balance and gait are affected. Neuropathic pain transitions to a burning sensation worsening at night. Over time, sensory deficit extends to the upper limbs, forearms, fingers and trunk and motor deficit follows with the same length dependent progression. At this stage, potentially life-threatening autonomic dysfunction is present manifesting as orthostatic hypotension, anhidrosis, neurogenic bladder, disturbances of gastrointestinal motility, and sexual impotence.

- Cardiac disease may occur in approximately 50% of patients with hATTR-PN. Ocular involvement is also common, including vitreous opacity, dry eye, glaucoma, and pupillary disorder.

- A rarer presentation of hATTR is leptomeningeal and meningovascular amyloidosis, often with concomitant vitreous opacity (oculoleptomeningeal amyloidosis). A number of mutations have reportedly been linked to this type of hATTR, though it may also manifest in more advanced cases of Val30MET hATTR-PN.

- Central nervous system symptoms include stroke, subarachnoid hemorrhage, dementia, ataxia, seizures, and sensorineural hearing loss.

- The source of mutant TTR in (oculo)leptomeningeal and meningovascular amyloidosis is thought to be the choroid plexus and retinal cells versus the liver. As such, ocular and meningovascular manifestations are commonly seen after liver transplantation because the source of mutant TTR is left unaffected.

- To date, no treatments have been proven to be beneficial for the treatment of (oculo)leptomeningeal and meningovascular amyloidosis.

- The 2013 guideline of transthyretin-related hereditary amyloidosis for clinicians recommends that the most reliable diagnostic approach involves genetic testing and tissue biopsy to confirm the presence of active amyloid formation. Genetic testing is needed to document the TTR gene mutations; if testing is normal, a diagnosis of hATTR is excluded.

- Options for treatment of hATTR are limited. Treatment strategies for hATTR include depletion of the source of mutant TTR, inhibiting TTR formation, stabilizing the TTR molecule from dissociating, and therapy directed at removing the amyloid deposits. Regardless of the choice of treatment, the 2013 guidelines and expert opinion from a panel of experts (2024) recommend initiation as soon as possible after diagnosis to slow or halt disease progression. The best outcomes have been shown in patients diagnosed at younger ages and/or without advanced disease.

- For hATTR-PN, our best treatment option historically had been orthoptic liver transplant, which removes the source of mutant TTR and was considered the gold standard for hATTR-PN treatment early in the course of disease. In hATTR-PN, the liver is the primary source of mutant TTR; transplantation eliminates approximately 95% of the production of mutant TTR and may slow or halt disease progression outside of the brain and/or eyes, though nerve function rarely improves post-transplant. Transplant does not effectively prevent cardiomyopathy, however, and is not recommended for patients with late stage hATTR-PN or leptomeningeal disease. With later stages of hATTR-PN and cardiomyopathy, there are concerns of disease progression due to deposition of wild-type TTR from the transplanted liver on the preexisting amyloid from the variant TTR.

- Numerous disease-modifying therapeutics are now available for hATTR-PN, including Amvuttra® (vutrisiran), Onpattro® (patisiran), and Wainua® (eplontersen). Guidelines have not yet been updated to include Amvuttra, Onpattro, and Wainua specifically; however, they do note that early

detection is critical and patients with early-stage disease should be treated with any approved drugs as they become available and as the patient's disease state meets drug indications, independent of liver transplant plans.

- Amvuttra, Onpattro, and Wainua are FDA-approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Of these products, only Wainua is FDA approved to be administered by the patient or caregiver; a healthcare provider is required for administration of Amvuttra and Onpattro per the approved labeling. To date, there is no literature supporting the use of one product over another, nor is there support for the use of any of these products together or in combination with other therapies approved for ATTR (e.g., tafamidis [Vyndamax® and Vyndaqel®], acoramidis [Attruby®]). The 2024 expert opinion does not offer recommendations on choice of specific treatment due to the lack of direct comparison trials and advises that clinicians consider the efficacy and safety considerations, in addition to any comorbidities and personal preferences around ease of use for an individual patient.

- Wainua is a ligand-conjugated antisense oligonucleotide (LICA) directed at TTR. It works by binding to and degrading TTR messenger RNA (mRNA) in the liver to prevent the production of TTR protein. Preventing TTR protein synthesis in the liver can help reduce the accumulation of amyloid deposits in peripheral nerves. Wainua works most similarly to Tegsedi, though it is thought to be engineered to be better at entering the liver which is the primary source of TTR.

- In the pivotal Phase III NEURO-TTRansform trial, patients treated with Wainua demonstrated consistent and sustained benefit on co-primary endpoints of serum TTR concentration and neuropathy impairment measured by the modified Neuropathy Impairment Score +7 (mNIS+7), and key secondary endpoint of quality of life (QoL) on the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN). The benefit of Wainua was demonstrated across the spectrum of hATTR-PN at 35, 66, and 85 weeks.

- In clinical trials, Wainua was only evaluated in patients with a baseline familial amyloid polyneuropathy (FAP) or Coutinho stage of 1 or 2. The FAP or Coutinho stage (stage 0-3) assesses the patient's level of ambulation and the severity/progression of neuropathy; stage 1 signifies ambulatory without assistance, and stage 2 is ambulatory with assistance. Wainua was not evaluated in patients with baseline FAP or Coutinho stage 3, which designates patients with late-stage, significantly advanced disease who are wheelchair-bound or bedridden; therefore, clinical trials do not support use in this patient population with advanced disease.

- The Polyneuropathy disability (PND) scoring system may also be used to classify hATTR-PN progression. This score focuses on the patient's walking ability, and scores range from 0 – IV. A PND score <IIIb equates to a FAP or Coutinho stage of 1 or 2, and a PND score of IV is considered equivalent to FAP or Coutinho stage 3.

- Patients who were receiving treatment with any approved drug for hATTR or off-label use of diflunisal or doxycycline, and those who had been previously treated with Onpattro or other oligonucleotide or RNA therapeutics were excluded from the clinical trial, as were those with a history

of liver transplant or NYHA functional classification of ≥3. There is no literature to support that patients who received a liver transplant would experience benefit from treatment with Wainua as they would not be expected to produce mutated TTR post-transplant.

- Additionally, there are no published clinical trials evaluating safety or efficacy of Wainua for the treatment of any condition other than hATTR-PN, and data is limited at this time on the effect of Wainua on other end organ dysfunction related to the underlying amyloidosis (i.e., cardiovascular outcomes).

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Policy History		
#	Date	Change Description
1.1	Effective Date: 06/05/2025	Reworded diagnosis criteria for clarity to align with approved labeling Removed criteria preventing use with previous liver transplant to align with management for other ATTR therapies
1.0	Effective Date: 03/01/2024	New Policy

Waskyra™ (etuvetidigene autotemcel)
HCPCS: J3590

Background Information:

- Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder caused by a mutation on the WAS gene. It is characterized by a dysfunctional WAS protein resulting in thrombocytopenia. The disease occurs almost exclusively in males.

- The symptoms of WAS typically begin in infancy and include bloody diarrhea, abnormal bleeding episodes, petechia, eczema, and recurrent ear infections. Thrombocytopenia), in association with small platelet size, is usually present at birth, but platelet counts may initially be near normal. Intracranial bleeding is a possible life-threatening complication. Children with WAS have an increased risk for recurrent bacterial and viral infections. Autoimmune disorders are also common in those who survive and include hemolytic anemia, arthritis, vasculitis, and kidney and liver damage. The risk for developing an autoimmune disorder increases with age. In addition, there is an increased risk of developing lymphomas, especially after exposure to Epstein-Barr virus.

- The 2015 practice parameter for the diagnosis and management of primary immunodeficiency state WAS should be suspected in all male patients with clinically significant thrombocytopenia and small platelets with platelet volumes ranging from 3.8 fL to 5.0 fL For a definitive molecular diagnosis, finding a known deleterious WAS mutation and/or abnormal WAS protein expression is necessary.

- A disease scoring system has been created that allows for clinical categorization of patients with WAS and may be useful in predicting disease severity and outcome of hematopoietic stem cell transplantation (HSCT). A score of 1 or 2 defines patients with X-linked thrombocytopenia (XLT), a score of 3 to 4 identifies patients with classic WAS, and a score of 5 is reserved for patients with either XLT or WAS after developing autoimmunity and/or malignancies. The clinical phenotype of the disease evolves over time and is often incomplete in males younger than two years of age. Because of this, WAS scores should not be used during infancy to predict disease severity. An established WAS score describes current disease severity and does not reflect the possibility of disease progression to a more severe form.

- Guidelines recommend HSCT be seriously considered for patients less than 5 years of age with suitable stem cell donors. If no stem cell donor is available, patients should be treated with supportive care including prophylaxis against PCP and appropriate antimicrobial therapy for infections, intravenous immunoglobulin, routine childhood immunizations, and treating eczema with topical steroid therapy. Treatment of significant bleeding sometimes includes platelet transfusions.

- Waskyra is the first disease modifying therapy approved for the treatment of pediatric patients aged 6 months and older and adults with WAS who have a mutation in the WAS gene for whom HSCT is appropriate and no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

- Safety and efficacy of Waskyra were evaluated in two clinical studies, study 1 and study 2, as well as an expanded access program. Study 1 was a prospective, open-label, single-arm trial of 8 patients with WAS that compared efficacy of Waskyra fresh formulation compared to 12 month pre-treatment outcomes. Study 2 is an ongoing, open-label, single-arm trial of 10 patients with WAS that is evaluating the efficacy of Waskyra cryopreserved formulation compared to 12 month pre-treatment outcomes. Subjects must have had a genetic mutation confirming diagnosis of WAS with at least one of the following: absence of WAS protein expression; a WAS clinical score greater than or equal to 3; or a severe WAS mutation. Participants did not have a matched HLA-identical sibling donor. Following treatment with rituximab and a reduced-intensity conditioning regimen of busulfan and fludarabine, patients received one intravenous infusion of Waskyra. The primary endpoints were the rate of severe infections during the 6 to 18 month period after Waskyra infusion compared with the 12-month pre-treatment period, and the rate of moderate or severe bleeding episodes during the 12-month period after Waskyra infusion compared with the 12-month pre-treatment period. The rate of severe infections decreased from 2.0 (95% CI: 1.50, 2.61) infections per patient year observation (PYO) in the 12 months pre-treatment period to 0.2 (95% CI: 0.04, 0.40) per PYO infections in 6 - 18 months post-gene therapy. The rate of moderate and severe bleeding events decreased from 2.0 (95% CI: 1.50, 2.61) events per PYO in the 12 months pre-treatment to 0.8 (95% CI: 0.49, 1.22) events per PYO in the 12 months after treatment

- Waskyra has not been studied and there is no data to support use in combination with other gene therapies indicated for use in WAS.

- Provider portal platforms allow the capture of clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.0	Effective Date: 02/12/2026	New policy

Yartemlea® (narsoplimab-wuug)
HCPCS: J3590

Background Information:

- Hematopoietic stem-cell transplantation–associated thrombotic microangiopathy (HSCT-TMA), also known as transplant-associated TMA, is a potentially fatal complication of HSCT. Disease pathogenesis is related to endothelial injury, which may be incited by factors that damage the endothelium and possible abnormalities of the alternative complement pathway. Damage to the endothelium can be caused by calcineurin inhibitors (CNI), chemotherapy, graft versus host disease (GVHD), total body irradiation, and/or infections. Several risk factors for the development of HSCT-TMA have been described including older age, female sex, advanced primary cancer disease, unrelated donor transplants, high-dose busulfan conditioning regimens, human leukocyte antigen (HLA) mismatch, nonmyeloablative transplants, total body irradiation, CNI use, mammalian (mechanistic) target of rapamycin (mTOR) inhibitor use in conjunction with CNI use, acute GVHD, and infection.

- HSCT-TMA usually develops within the first 100 days after transplantation but may have a later onset in some patients. Patients typically present with microangiopathic hemolytic anemia along with thrombocytopenia, an elevated serum lactate dehydrogenase (LDH) level, and the presence of schistocytes on the peripheral blood smear. Serum haptoglobin is often low but may be normal or elevated in some patients. Kidney manifestations include an acute or subacute rise in the serum creatinine concentration and a urinalysis that may be relatively normal or show variable proteinuria and/or hematuria. Hypertension is often present.

- HSCT-TMA can range from a mild, self-limited form to severe, uncontrolled disease that frequently results in death. The reasons for this variation in disease severity are unclear but may be related to factors involving the recipient, the donor, or inciting events such as infections. In most patients, the hematologic abnormalities eventually resolve, although hypertension and chronic kidney disease (CKD) usually persist. Some patients progress to end-stage kidney disease (ESKD). Other patients may develop multiorgan involvement including pulmonary hypertension, polyserositis, gastrointestinal symptoms, and central nervous system injury.

- Diagnosis should be suspected in HSCT recipients who present with one or more of the following: elevated serum LDH level; elevated serum creatinine; new-onset or increasing proteinuria; hypertension that is out of proportion to what would be expected from CNI and glucocorticoid therapy or volume overload; and/or a sudden requirement for more transfusion support than previously needed to maintain stable blood cell and platelet counts. There is no current standard definition of HSCT-TMA; however, the 2005 Blood and Marrow Transplant Clinical Trials Network Toxicity Committee proposed an operational definition that includes the following: red blood cell fragmentation with greater than 2 schistocytes per high-power field on peripheral smear; concurrent increased serum lactate dehydrogenase above institutional baseline; concurrent renal and/or neurologic dysfunction without other explanations, where renal dysfunction is defined as either a doubling of serum creatinine from baseline, where baseline is the creatinine taken before hydration and just before initiation of the conditioning regimen, or a 50% decrease in creatinine clearance from baseline; and negative direct and indirect Coombs test results. In cases in which the diagnosis is uncertain based upon clinical findings, a kidney biopsy may be helpful to establish the diagnosis although the ability to perform a kidney biopsy is often limited by the presence of thrombocytopenia.

- There are no treatment guidelines for HSCT-TMA. The optimal approach to treatment is not known. Management is largely supportive and focuses on the management of hypertension and transfusion support as appropriate. Patients with hypertension should receive antihypertensive agents to control blood pressure. The optimal antihypertensive agent is unclear; however, in patients with proteinuria, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) would be most appropriate. Discontinuation of CNIs and/or sirolimus is not generally recommended since there is no evidence that discontinuing these agents is clearly beneficial to patients with HSCT-TMA and increase the risk of GVHD. However, in patients who present with acute kidney injury (AKI), it may be beneficial to withdraw or reduce the dose of CNI and/or sirolimus if no other underlying cause for HSCT-TMA can be identified and the blood CNI level is higher than expected. If the decision is made to withdraw the CNI and/or sirolimus, replacement with mycophenolate mofetil with or without glucocorticoids may be reasonable. Other replacement options include interleukin (IL) 2 receptor antagonists.
- In patients with severe HSCT-TMA with kidney, cardiac, or pulmonary involvement that progresses in spite of general supportive measures, potential therapeutic options include Rituxan®, Soliris®, and Defitelio®. Evidence to support their efficacy is limited to mostly small observational studies and use of these agents should be considered on a case-by-case basis as none of these medications are indicated for use in HSCT-TMA. In patients with severe, progressive HSCT-TMA with multiorgan involvement who have evidence of complement activation, Soliris would be the preferred option. Rituxan should be considered in patients with primarily kidney involvement and no evidence of complement activation. Defitelio should be reserved for patients who do not respond to either Soliris or Rituxan.

- Yartemlea is a MASP-2 inhibitor indicated for the treatment of adult and pediatric patients 2 years of age and older with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA).

- Safety and efficacy of Yartemlea were evaluated in the TA-TMA trial, a single-arm, open-label study in 288 adults with HSCT-TMA. The results were supported by additional data from an expanded access program (EAP) of 19 evaluable adult and pediatric patients aged 2 years and older. In the TA-TMA study, 24 patients received 4 mg/kg Yartemlea once weekly and 4 patients received 370 mg Yartemlea once weekly. The median number of Yartemlea administrations received by the 28 TA-TMA trial patients plus the 19 EAP patients was 8 (range: 2 - 34) with a median duration of therapy of 8 weeks (range: 2 - 16 weeks). Study patients had a confirmed diagnosis of HSCT-TMA when meeting all of the following for a period greater than or equal to 2 weeks after modification or discontinuation of CNI therapy or greater than or equal to 30 days after transplantation: platelet count less than 150 x 10^9/L; evidence of microangiopathic hemolysis defined by the presence of schistocytes, serum lactate dehydrogenase (LDH) above the ULN, or haptoglobin below the lower limit of normal; and kidney dysfunction defined as a doubling of serum creatinine from pretransplant. The primary endpoint was based on HSCT-TMA response defined as improvement in both LDH and platelet counts and either improvement in organ function or independence from transfusions. Improvement in platelet count when patients had a baseline count of less than or equal to 20,000/µL was defined as greater than or equal to a 3-fold increase in platelet count, post-baseline platelet count greater than 30,000/µL, and no platelet transfusions within 2 days prior to the platelet count assessment. Improvement in platelet count when patients had a baseline count of greater than or equal to 20,000/µL was defined as greater than or equal to a 50% increase in platelet count, platelet count greater than 75,000/µL, and no platelet transfusions within 2 days prior to the platelet count assessment. To meet LDH improvement criteria, LDH levels were required to be less than 1.5 times the upper limit of normal. In the TA-TMA study and the EAP, HSCT-TMA response was achieved in 17/28 (60.7%) and 13/19 (68.4%) patients, respectively. Across the TA-TMA study and the EAP, 100-day survival from the time of HSCT-TMA diagnosis was 73% (95% CI: 52, 86) and 74% (95% CI: 48, 88) respectively.

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Policy History		
#	Date	Change Description
1.0	Effective Date: 02/12/2026	New policy

Yervoy® (ipilimumab)
HCPCS: J9228

Background Information:

- Yervoy is currently indicated for use as monotherapy in patients 12 years of age or older and as combination therapy with Opdivo in patients 12 years of age or older for unresectable or metastatic melanoma; as adjuvant treatment in patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy; in combination with Opdivo in advanced renal cell carcinoma; in combination with Opdivo in patients age 12 and older for metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer; in combination with Opdivo for patients 18 years of age or older with hepatocellular carcinoma in patients previously treated with sorafenib or as first-line therapy; in combination with Opdivo for patients 18 years of age or older with previously untreated metastatic non-small cell lung cancer; in combination with Opdivo and platinum-doublet chemotherapy for patients 18 years of age or older with previously untreated advanced or metastatic non-small cell lung cancer; in combination with Opdivo for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma; and in combination with Opdivo for the first-line treatment of adult patietns with unresectable advanced or metastatic esophageal squamous cell carcinoma.

- Unresectable or metastatic melanoma

    - The safety and efficacy of Yervoy as mootherapy were investigated in a randomized (3:1:1), doubleblind, double-dummy trial of 676 patients with previously treated unresectable or metastatic melanoma. Patients were randomized to receive either Yervoy or an investigational peptide vaccine with (gp100). The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression and those with an ECOG score greater than 1. Yervoy or placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses. Yervoy was found to improve overall survival versus gp100 alone (10.0 months and 10.1 months versus 6.4 months, $p<0.001$ and $p=0.003$, respectively).

- As adjuvant therapy for cutaneous melanoma

    - The EORTC 18071 trial was a randomized, double-blind, placebo-controlled trial conducted with 951 high-risk patients with stage IIIA (> 1 mm nodal involvement, IIIB, and IIIC melanoma who had undergone complete lymphadenectomy. Patients were randomized to receive Yervoy 10 mg/kg or placebo as an intravenous infusion every 3 weeks for 4 doses, followed by Yervoy 10 mg/kg or placebo every 12 weeks from Week 24 to Week 156 (3 years) or until documented disease recurrence or unacceptable toxicity. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression and those with an ECOG score greater than 1. In the 475 patients who received a regimen with 10 mg/kg ipilimumab, median recurrence-free survival was 26.1 months, versus 17.1 months in the placebo group ($p=0.0013$).

- Advanced renal cell carcinoma

    - The CheckMate 214 trial was a randomized, open-label study with 1096 patients with renal cell carcinoma that were previously untreated, 847 of those were classified as intermediate- or poor-risk patients. Immediate or poor risk is defined as one or more of the following: less than one year from the time of diagnosis to the start of systemic therapy, Karnofsky performance status of < 80%, hemoglobin < 12 g/dL, calcium > 10.2 mg/dL, neutrophils > 7.0 x 10^9/L, or platelets > 400,000/mcL. Patients received (1:1) either Yervoy plus Opdivo or sunitinib every 3 weeks for 12 weeks. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression and those with an ECOG score greater than 1. While the median progression-free survival of Yervoy plus Opdivo compared to sunitinib did not meet the prespecified significance threshold of p = 0.009 (11.6 months and 8.4 months respectively, p = 0.03), overall survival (not met and 26.0 months, p < 0.001) and objective response rate (42% and 27%, p < 0.001) were significantly improved in the Yervoy plus Opdivo group as compared to the sunitinib group.

- Metastatic, microsatellite instability-high or mismatch repair deficient colorectal cancer

    - The CheckMate-8HW trial was a randomized, 3 arm, open-label study of 303 patients with dMMR or MSI-H metastatic CRC. In the Yervoy + Opdivo cohort 202 patients received Opdivo 3 mg/kg and Yervoy 1 mg/kg every 3 weeks for four doses then Opdivo 3 mg/kg every 2 weeks. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression and those with an ECOG score greater than 1. The primary endpoint was progression free survival (PFS). Disease progression or death was seen in 28% of patients in the Opdivo + Yervoy arm compared to 62% of the participants in the chemotherapy arm which was statistically significant (p-value < 0.0001).

- Hepatocellular carcinoma

    - The Checkmate-040 trial was a multicenter, multiple cohort, open-label trial study of 1097 patients with HCC who progressed on or were intolerant to sorafenib. Patients in cohort 4 received Yervoy 3 mg/kg every 3 weeks for 4 doses in combination with Opdivo every 2 weeks until disease progression or unacceptable toxicity. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression and those with an ECOG score greater than 1. NCCN guidelines for hepatocellular carcinoma recommend use only in Child-Pugh class A patients. The overall response rate was 33% with a complete and partial response in 8% and 24% of patients respectively.

    - The Checkmate-9DW trial was a randomized, open-label trial of 668 patients with previously untreated unresectable or metastatic HCC. Patients were randomized to either 3 mg/kg Yervoy in combination with 1 mg/kg Opdivo every 3 weeks for a maximum of 4 doses, followed by single agent Opdivo at 480 mg every 4 weeks or 8 mg lenvatinib daily or 400 mg sorafenib twice daily. The trial excluded

patients with active autoimmune disease or those receiving systemic immunosuppression and those with an ECOG score greater than 1. NCCN guidelines for hepatocellular carcinoma recommend use only in Child-Pugh class A patients. The study demonstrated a statistically significant improvement in OS and ORR.

- Metastatic non-small cell lung cancer

    - The Checkmate-227 trial was a randomized, open-label, multi-part trial in patients with in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations. In part 1a of the trial, 793 patients with PD-L1 tumor expression ≥ 1% were randomized to receive either Yervoy 1 mg/kg every 6 weeks and Opdivo 3 mg/kg every 2 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression and those with an ECOG score greater than 1. The primary endpoints were overall survival and progression free survival. The median overall survival was 17.1 months and 14.9 months for the Yervoy/Opdivo arm and platinum chemotherapy arm respectively (p=0.0066). Median progression-free survival was 5.1 months in the Yervoy/Opdivo arm and 5.6 months in the platinum chemotherapy arm (HR 0.82; 95% CI: 0.69, 0.97).

    - The Checkmate 9LA was a randomized, open-label trial in patients 18 years of age or older with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations. Patients were enrolled regardless of their tumor PD-L1 status. Patients were randomized to receive Yervoy 1 mg/kg every 6 weeks and Opdivo 360 mg every 3 weeks and platinum-doublet therapy every 3 weeks for 2 cycles or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The trial excluded patients with active autoimmune disease, those receiving systemic immunosuppression, and those with an ECOG score greater than 1. The primary endpoint was overall survival. The study demonstrated a statistically significant benefit in overall survival, progression free survival, and overall response rate.

    - Malignant pleural mesothelioma

    - The Checkmate-743 trial was a randomized, phase III, open-label trial of 605 patients age 18 years and older with unresectable pleural mesothelioma. Patients were previously untreated and not eligible for curative surgery. Patients were randomized to receive Yervoy 1 mg/kg every 6 weeks and Opdivo 3 mg/kg every 2 weeks for up to 2 years or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2, or carboplatin 5 AUC and pemetrexed 500 mg/m^2 administered every 3 weeks for 6 cycles. The trial excluded patients with active autoimmune disease, those receiving systemic immunosuppression, and those with an ECOG score greater than 1. The primary endpoint was overall survival. The study demonstrated a statistically significant benefit in overall survival in the Yervoy arm compared to the placebo arm (p-value = 0.002).

- Unresectable advanced or metastatic esophageal squamous cell carcinoma

- The Checkmate-648 study was a randomized, active-controlled, open-label trial of 649 patients with previously untreated unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma. Patients were randomized to receive Yervoy 1 mg/kg every 6 weeks in combination with Opdivo 3 mg/kg every 2 weeks or fluorouracil 800 mg/m^2/day days 1 through 5 and cisplatin 80 mg/m^2 day 1 of a 4-week cycle. Patients were excluded if they had brain metastasis, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor. The primary endpoint was overall survival. The study demonstrated a significantly significant benefit in overall survival in the Yervoy are compared to the comparator are (p-value = 0.0110).

- There are no studies to support use of Yervoy following failure of its use as a single agent or in combination with a PD-L1 checkpoint inhibitor, such as Opdivo. NCCN guidelines also do not recommend use of Yervoy or PD-L1 checkpoint inhibitors following a previous failure.

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Policy History		
#	Date	Change Description
1.7	Effective Date: 08/07/2025	Updated to include the requirement that tumors express PD-L1 ≥ 1% for unresectable advanced or metastatic esophageal squamous cell carcinoma
1.6	Effective Date: 06/05/2025	Updated to include the new indications for use in unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) in combination with nivolumab and for use as first-line therapy in hepatocellular carcinoma and include the trial and failure of preferred products statement
1.5	Effective Date: 04/10/2025	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 04/06/2023	Updated to include the updated age requirements when used to treat melanoma

1.2	Effective Date: 12/01/2022	Updated to include the new indication of esophageal cancer and update the approval length to allow for FDA recommended dosing and provided for at least 60 days up to 6 months at a time
1.1	Effective Date: 12/09/2021	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 01/01/2021	New Policy

Yescarta™ (axicabtagene ciloleucel)
HCPCS: Q2041

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

    - Yescarta is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for the treatment of patients with primary central nervous system lymphoma. Yescarta is also indicated for adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

    - Efficacy was established in a single-arm, open-label, multicenter trial of 111 adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Of 111 patients who underwent leukapheresis, 101 received Yescarta. One patient did not receive the product due to manufacturing failure and 9 others were not treated due to progressive disease or serious adverse reactions. Yescarta was administered as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T-cells/kg. The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously given on the fifth, fourth, and third day before Yescarta. Patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection were excluded. Subjects had previously received an anti-CD20 monoclonal antibody containing-regimen and an anthracycline-containing chemotherapy. Patients with transformed FL had received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL. Primary endpoints were complete remission rate and duration of response.

The median time to response was 0.9 months (range: 0.8 to 6.2 months). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

- Safety and efficacy for use in FL and MZL were established in the ZUMA-5 trial, an ongoing single-arm, open-label, multicenter phase 2 study of 104 adult patients with relapsed/refractory indolent NHL who had received up to 2 prior lines of therapy, including an anti-CD20 monoclonal antibody combined with an alkylating agent. Of the 104 patients, 84 had follicular lymphoma and 20 patients had marginal zone lymphoma and were required to have measurable disease. Patients were excluded if they had prior allogeneic HSCT, any history of central nervous system disease, ECOG performance status of 2 or greater, transformed FL, histological grade 3b FL, inadequate renal, hepatic, or cardiac function, or active serious infection. The primary endpoint is the objective response rate to therapy and key secondary endpoints include duration of response, progression-free survival (PFS), overall survival (OS), and incidence of adverse events. After a median follow-up of 17.5 months, the objective response rate was 92% with 76% of patients reaching a complete response. When broken down by exact indication, 94% (n = 84) of patients with relapsed/refractory FL had an objective response including 80% achieving a complete response. Of patients with relapsed/refractory MZL (n=20), 85% had an objective response with 60% achieving a complete response. At the data cutoff, 62% of all treated patients had ongoing responses. Median duration of response (DOR), progression-free survival (PFS) and overall survival (OS) were not reached.

- Safety and efficacy for use as second-line therapy in relapsed or refractory DLBCL is being established in the ZUMA-7 trial, an ongoing phase 3, randomized, open-label, multicenter study of 359 patients with replased/refractory DLBCL who had received one prior line of therapy that included an anti-CD20 monoclonal antibody combined with an anthracycline agent. Patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection were excluded. Relapsed disease was defined as complete remission to first-line therapy followed by biopsy-proven relapse ≤ 12 months of first-line therapy. Refractory disease was defined as no complete remission to first-line therapy: progressive disease (PD) as best response to first-line therapy; stable disease (SD) as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP); or partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy. The primary endpoint is event-free survival (EFS) defined as time from randomization to disease progression, start of new lymphoma therapy, or death. ZUMA-7 met its primary EFS endpoint demonstrating statistically significant and clinically meaningful improvement in efficacy with Yescarta vs second-line standard of care.

- While use of Yescarta has not been established in patients with a creatinine clearance of less than 60 mL/minute, other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other

CAR-T therapies support their use in these patients, Yescarta should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 ml/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.

- While use of Yescarta has not been established in patients with an alanine aminotransferase of greater than 2.5 times the upper limit of normal (ULN), other CAR-T therapies have been studied in subjects with an alanine aminotransferase of up to 5 times the ULN and the CTCAE recommendations have set 5 times the ULN as the cutoff for grade 2 adverse reactions. As the classification system uses 5 times the ULN and other CAR-T therapies have data supporting use in this patient population, Yescarta should be tolerated in these patients as well. As there is no data to support administration of CAR-T at levels higher than 5 times the ULN, therapy should not be given to patients not meeting that threshold.

- The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. While Yescarta has only been studied in patients with a LVEF greater than or equal to 50%, there is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Yescarta should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.

- A provider portal that is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.5	Effective Date: 06/06/2024	Annual review of criteria was performed, no changes were made
1.4	Effective Date: 08/04/2022	Updated to align criteria across all CAR-T policies
1.3	Effective Date: 06/09/2022	Updated to include new indication allowing for use second-line in relapsed/refractory large B-cell lymphoma
1.2	Effective Date: 02/10/2022	Updated to include preliminary criteria for use as second-line therapy for DLBCL and remove the CD19 positive requirement
1.1	Effective Date: 08/12/2021	New policy
1.0	Effective Date: 01/01/2021	New Policy

Zevaskyn™ (prademagene zamikeracel)
HCPCS: J3389

Background Information:

- Epidermolysis bullosa, or EB, is a rare, inherited connective tissue disorder that causes abnormalities in cohesion of layers of the skin. There are 4 different types of EB, one of which is dystrophic epidermolysis bullosa (DEB) which makes up about 25% of EB cases. DEB can be inherited dominantly or recessively, with recessive cases being the most common and most severe. Patients with dominant DEB have few complications and survive into adulthood, while those with recessive only live to their 3rd or 4th decade, often dying of squamous cell carcinoma or renal failure.

- DEB is caused by mutations in the *COL7A1* gene which codes for Type 7 collagen, whose responsibility is to bind the dermis to the epidermis. In DEB, Type 7 collagen is either reduced or completely absent, creating extremely fragile skin that blisters between the dermis and the epidermis and tears from even the most minor friction or trauma, such as holding a pencil or putting on a shirt. The constant cycle of blistering, wounding, and re-healing that occurs with DEB contributes to complications like infection, debilitating scarring, physical deformities, pubertal or growth delay, anemia, esophageal blistering, spinal fractures, and squamous-cell carcinoma.

- Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa developed on behalf of the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International (2020) recommend every patient with an established or suspected diagnosis of EB undergo genetic testing (level of evidence 2++, grade of recommendation B). Skin biopsy of an induced blister with immunofluorescence mapping (IFM) and/or transmission electron microscopy (TEM) may also be useful in the diagnosis of EB; however, with DEB, particularly in mild cases, the results of these tests may not deliver a useful result and genetic testing documenting the presence of mutations in the *COL7A1* gene would be required to deliver the final diagnosis.

- The goal of treatment is to promote wound healing, prevent infection and other complications, and protect the skin. Prior to the FDA approval of DEB therapies, there were no approved treatments for any form of EB. Management has historically been supportive, involving a multidisciplinary team that includes wound care, infection and pain control, nutritional support, and prevention and treatment of complications.

- A consensus statement from the European Reference Network for Rare Skin Diseases on the practical management of EB (2021) and an international consensus on best practice guidelines for skin and wound care in EB from Wounds International (2017) regard wound care as the cornerstone of treatment for EB patients. Skin and wound assessments should be undertaken regularly and management tailored to suit both the type of EB and the specific characteristics of the wound, as well as the needs and preferences of the patient. Regular follow up on patient

and caregiver adherence to treatment should also be performed with adaptation of the care plan to meet the patient's needs and preferences, as needed.

- Malnutrition, anemia, pruritus, and pain can compromise a patient's ability to heal; therefore, these conditions should be treated appropriately to optimize long-term wound healing and minimize further skin damage and trauma.

- Atraumatic dressings should be utilized to prevent blistering and skin and wound bed damage. Dressing examples include polymeric membrane, super-absorbent, soft silicone mesh or foam, lipido-colloid, foam, and keratin. Most dressings should be changed every 1 to 3 days unless otherwise noted by the manufacturer or required by the patient's individual needs.

- Preventative measures to avoid and/or reduce blister formation should also be enforced, such as padding trauma-exposed sites, avoidance of tight clothing, choosing suitable footwear with appropriate insoles and/or orthotics. Any intact blisters should be lanced and drained as they are not self-limiting.

- Wound management in DEB must also address infection, critical colonization, and protection from additional trauma. Bacterial burden can be controlled by systemic or topical therapies.

- Healing rate of wounds should be monitored by checking advancement of the wound edges. A reduction of 20-40% in 2 to 4 weeks may predict healing by 12 weeks. Pain and itch reduction and resolution of infection should also be evaluated.

- Recently approved treatments for DEB include topical gene therapy Vyjuvek® for the treatment of wounds in patients with DEB and mutations in the *COL7A1* gene, Filsuvez®, a topical gel that promotes general wound healing of DEB-associated wounds, and Zevaskyn, an autologous cell sheet-based gene therapy for the treatment of wounds in adults and pediatric patients with RDEB. All three products work locally to heal open skin wounds and do not treat extracutaneous manifestations of DEB; therefore, supportive and palliative care will continue to remain essential even in patients receiving treatment with FDA-approved therapies.

- Zevaskyn consists of a patient's own cells that have been gene-modified through retroviral vector (RVV) transduction to express the *COL7A1* gene to produce the collagen 7 (C7) protein. These cells are formed into cellular sheets for topical application onto wounds. It is the only FDA-approved product to treat RDEB wounds with a one-time surgical application. The use of Zevaskyn has not yet been addressed by any guidelines or consensus statements.

- The safety and effectiveness of Zevaskyn was established primarily in the pivotal, randomized, intrapatient-controlled Phase III VIITAL study, which compared Zevaskyn to standard of care (SOC) treatment in patients with RDEB wounds. Eligible patients were 6 years of age and older

and required to have at least one pair of matched, large (≥ 20 cm^2), chronic (open for ≥ 6 months) stage 2 wounds associated with RDEB. Stage 2 wounds are typically shallow with a reddish base and are characterized by partial-thickness skin loss into, but no deeper than, the dermis.

- The matched wound pairs were randomized 1:1 to receive either Zevaskyn (up to 6 sheets) or control treatment consisting of SOC wound dressings and palliative care. Eleven patients ranging from 6 to 40 years old were enrolled and a total of 86 wounds were randomized to treatment.

- The co-primary endpoints were the proportion of randomized wound pairs with at least 50% healing at 6 months with confirmation of wound healing two weeks later, and pain reduction as accessed by the mean differences in patient-reported pain scores using the Wong-Baker FACES® scale between randomized wound pairs at 6 months.

- The trial met its co-primary endpoints. With Zevaskyn treatment, 81% of wounds (35/43) showed 50% or more healing at 6 months compared to 16% (7/43) in SOC-treated wounds. Additionally, Zevaskyn treatment demonstrated a nearly 3.5-times reduction in pain versus matched control wounds as reported following wound dressing changes using the Wong-Baker FACES pain rating scale (3.1-point reduction vs. 0.9-point reduction, respectively, utilizing a scale of 0-10; p=0.0002).

- Up to 12 Zevaskyn sheets may be manufactured per patient per treatment cycle, with each sheet covering an area of 41.25 cm^2. The recommended dose is based on wound surface area. Zevaskyn sheets are surgically applied to the wound(s) in a single surgical session at a qualified treatment center by a qualified healthcare provider and must not be trimmed. Only once Zevaskyn treatment cycle is recommended per treatment area. If different areas develop that necessitate treatment, a patient may then require more than one cycle.

- Additional gene and cell therapies are in development for the treatment of DEB. At present, there is no literature to support combination use of multiple gene therapies for the treatment of DEB

- Provider portals are used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

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Policy History		
#	Date	Change Description
1.1	P&T Date: 10/09/2025 Effective Date: 11/24/2025	Changed wound area requirement from >20 cm2 to >200 cm2 Modified the criterion preventing combination use of RDEB gene therapies on the same wound to also include prior treatment with Zevaskyn
1.0	Effective Date: 09/01/2025	New Policy

Zilretta® (triamcinolone acetonide extended-release)
HCPCS: J3304

Background Information:

- Osteoarthritis (OA) is a common degenerative condition affecting the knees. Historically a disease of older Americans, OA is now being diagnosed at increasingly younger ages with the prevalence rising after age 45. More than 27 million individuals are affected by osteoarthritis. By 2030 it is expected to affect 67 million Americans.

- The overall goals of management are to reduce pain and prevent disability. Rheumatologists and orthopedists are the primary physician specialties versed in handling musculoskeletal disorders like OA, especially in cases of complicated or treatment-refractory disease. Consulting an orthopedic surgeon may be necessary for cases that may require surgical intervention.

- The American College of Rheumatology (ACR), American Academy of Orthopedic Surgeons (AAOS), and the Osteoarthritis Research Society International (ORSI) have practice guidelines for the management of OA of the knee. These guidelines provide recommendations for both non-pharmacologic and pharmacologic therapies for the treatment of knee OA.

- The ACR, AAOS, and ORSI all agree that non-pharmacologic treatment is a mainstay of therapy for all patients with knee OA. Non-pharmacologic treatment modalities are often used in combination to maximize their effectiveness.

    - Exercise is strongly recommended for all patients with OA, with an emphasis on resistance training (i.e. weightlifting, band exercises) and cardiovascular/aerobic exercise (i.e. walking, stationary bicycles, aquatics). Exercise interventions have evidence to support statistically and clinically significant improvements in pain and function scores in OA.

    - Weight loss is also recommended for patients with knee OA who are overweight (defined as a BMI $\geq$ 25). The 2019 ACR guidelines specifically note that a loss of $\geq$ 5% of body weight can yield positive change in clinical and mechanistic outcomes; the benefits continue to increase as the percent of weight lost increases.

    - Gait aids may be warranted for use in knee OA . The 2019 ACR guidelines strongly recommend the use of a cane and tibiofemoral knee braces in the event the disease is significantly impacting ambulation, joint stability, or pain; kinesiotaping and patellofemoral braces are conditionally recommended. The 2021 AAOS guidelines suggest braces and canes could help improve pain and function in patients with knee OA with moderate strength evidence.

    - Physical and occupational therapy have also shown evidence of benefit in knee OA, particularly for initiating and maintaining an appropriate exercise regimen, for self-efficacy and self-management training, and instruction in the use of and fitting of braces.

- Pharmacologic interventions strongly recommended by the ACR, AAOS, and OARSI for knee OA include topical and oral NSAID therapy. Oral NSAIDs should be avoided in patients of any age with conditions putting them at high risk of cardiovascular, renal, gastrointestinal, and hematologic adverse events associated with NSAID use. The elderly population (65 years of age and older) in particular are very susceptible to the side effect profiles of NSAIDs; NSAIDs have also been shown to increase the risk of falls, geriatric psychiatric events, and the risk of stroke in elderly patients.

- Intra-articular glucocorticoid injections are recommended for knee OA by the ACR and OARSI recommendations (strongly recommended and conditionally recommended, respectively), and most recently by the AAOS per the updated 2021 guidelines as they have demonstrated short-term efficacy in symptomatic knee OA. Intra-articular glucocorticoid injections are available in both short- and long-acting preparations; however, there is insufficient evidence evaluating comparative safety and efficacy to recommend one product over the other.

- Zilretta (triamcinolone acetonide extended-release) is an extended-release intra-articular corticosteroid injection indicated for the management of osteoarthritis pain of the knee.

    - It is administered as a one-time injection into the affected knee(s); the safety and efficacy of repeat injections have not been demonstrated.

    - Per the prescribing information, the safety and effectiveness of Zilretta in pediatric patients has not been established; therefore, use is limited to patients 18 years of age and older.

    - The safety and efficacy of Zilretta have not been evaluated for the management of osteoarthritis of other joints besides the knees.

- A Phase 3 trial demonstrated statistically significant improved pain, stiffness, and function in patients with osteoarthritis of the knee (Kellgren-Lawrence grade 2 or 3) treated with Zilretta compared to placebo through 12 weeks post injection. The treatment arm comparing Zilretta to traditional intraarticular triamcinolone acetonide, however, showed a similar onset of action and no statistically significant pain relief superiority between the two agents.

- The use of Zilretta in patients with previous intraarticular corticosteroid injections in any joint within 3 months of treatment with Zilretta was not established in the Phase 3 trial as these patients were excluded from enrollment.

- Zilretta has not demonstrated superior efficacy over traditional short-acting intra-articular triamcinolone acetate. There is a lack of data supporting one preparation over the other and a significant difference in cost between Zilretta and generically available intraarticular triamcinolone acetonide. This supports requiring trial and failure of short-acting intraarticular triamcinolone prior to Zilretta, as well as requiring a credible explanation to why the long-acting formulation is expected to work if the short-acting formulation of the same product resulted in treatment failure.

References:

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Policy History		
#	Date	Change Description
1.4	Effective Date: 08/07/2025	Annual review of criteria was performed, no changes were made

1.4	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 08/10/2023	Removed prescriber requirement from criteria
1.2	Effective Date: 08/04/2022	Annual review of criteria was performed, no changes were made
1.1	Effective Date: 08/12/2021	Annual review of criteria was performed, no changes were made
1.0	Effective Date: 11/01/2021	New Policy

Zinplava™ (bezlotoxumab)
HCPCS: J0565

Background Information:

- Zinplava is a human monoclonal antibody that binds to Clostridium difficile toxin B, indicated to reduce recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.

- CDI is one of the most common hospital-acquired (nosocomial) infections and is an increasingly frequent cause of morbidity and mortality among older adult hospitalized patients. Clostridium difficile colonizes the human intestinal tract after the normal gut flora has been altered by antibiotic therapy and is the causative organism of antibiotic-associated pseudomembranous colitis.

- Patients taking antibiotics are 7 to 10 times more likely to contract CDI. The overprescribing of antibiotics combined with poor hygiene and infection control on the part of healthcare workers make CDI a scourge in the nation's hospitals and nursing homes.

- Toxins A and B are the major virulence factors of Clostridium difficile. Toxins A and B mediate disease by disrupting the cytoskeletal structure of intestinal epithelial cells, resulting in inflammation and cell death. Toxin A ("enterotoxin") causes inflammation leading to mucosal injury and intestinal fluid secretion. Toxin B ("cytotoxin") is essential for the virulence of Clostridium difficile and is more potent than toxin A in mediating colonic mucosal damage. Ribotype 027 is a hypervirulent strain of Clostridium difficile found in 87% of patients who had a hypervirulent strain in the Zinplava study.

    - The 2021 Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) Guideline Update recommends use of adjunctive therapy for prophylaxis after one recurrent CDI episode treated with appropriate antibiotics.

        - These guidelines recommend the use of Zinplava for patients with recurrent CDI episode within the last 6 months, as an adjunctive treatment to antibiotics (fidaxomicin, vancomycin, etc.) rather than antibiotics alone. Zinplava is an IV administered monoclonal antibody that is given as a single infusion over 60 minutes.

        - The guidelines state the balance of benefits and harms favor adding Zinplava to standard of care antibiotics for patients with a CDI episode and at least 1 risk factor for recurrence (recurrent CDI episode within the last 6 months, age ≥ 65 years, immunocompromised host, and severe CDI on presentation), however treatment seems more favorable in patients with multiple risk factors of recurrent CDI and especially in patients with a prior CDI in the last 6 months. Current guidelines do not favor the use of Zinplava or fecal microbiota transplantation (FMT) over the other for prevention of recurrence of CDI. Zinplava was the only FDA approved option for prevention of recurrence of CDI when the 2021 IDSA/SHEA guidelines were published.

- In Zinplava's Phase III trial, standard of care antibiotics used were metronidazole (48%), vancomycin (48%), and fidaxomicin (4%).

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3. Bezlotoxumab (BEZ) Alone and With Actoxumab (ACT) for Prevention of Recurrent C. difficile Infection (rCDI) in Patients on Standard of Care (SoC) Antibiotics: Integrated Results of 2 Phase 3 Studies (MODIFY I and MODIFY II) Open Forum Infect Disease, Fall 2015, Vol 2, issue suppl 1.
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Policy History		
#	Date	Change Description
1.5	Effective Date: 05/27/2025 P&T Date: 04/10/2025	Updated criteria to include: Not to be used in combination with fecal microbiota products, such as Rebyota or Vowst
1.4	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
1.3	Effective Date: 04/06/2023	Updated the approval duration to allow for 60 day requirement
1.2	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made.
1.1	Effective Date:	Annual review of criteria was performed, no changes were made.

	04/08/2021	
1.0	Effective Date: 01/01/2021	New Policy