Effective Date: 10/03/2024

Eculizumab Products

Bkemv™ (eculizumab-aeeb)
Epysqli® (eculizumab-aagh)
Soliris® (eculizumab)

HCPCS: Bkemv: J3590; Epysqli: J3590; Soliris: J1300

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Documented diagnosis of paroxysmal nocturnal hemoglobinuria (PNH)
      i. Flow cytometric confirmation of PNH type III red cells
      ii. Had at least 1 transfusion in 24 months preceding eculizumab
      OR
      iii. Documented history of major adverse thrombotic vascular events from thromboembolism
      OR
      iv. Patient has high disease activity defined as a lactic dehydrogenase (LDH) level ≥ 1.5 times the upper limit of normal with one of the following symptoms:
         1. Weakness
         2. Fatigue
         3. Hemoglobinuria
         4. Abdominal pain
         5. Dyspnea
         6. Hemoglobin < 10 g/dL
         7. A major vascular event
         8. Dysphagia
         9. Erectile dysfunction
      v. Trial and failure, contraindication, or intolerance to Empaveli™
      vi. Must not be used in combination with Ultomiris®, Empaveli™, or other medications to treat PNH
   c. For a diagnosis of atypical hemolytic uremic syndrome (aHUS)
      i. Common causes of typical hemolytic uremic syndrome have been ruled out, including infectious causes of HUS and thrombotic thrombocytopenic purpura (TTP)
      ii. Must present with the following symptoms:
         1. Hemoglobin < 10 g/dL
         2. Platelets < 150,000/mm^3
         3. Documented evidence of hemolysis, such as, elevated lactate dehydrogenase levels,

decreased haptoglobin level, or schistocytosis
4. Increased serum creatinine OR currently undergoing dialysis

iii. Must not be used in combination with Ultomiris or other medications to treat aHUS

d. Diagnosis of refractory generalized myasthenia gravis (MG)
   i. Documented diagnosis of refractory, anti-acetylcholine receptor (AChR) antibody positive MG identified by:
      1. Lab record or chart notes identifying the patient is positive for anti-AChR antibodies AND
      2. One of the following confirmatory tests:
         a) Positive edrophonium test
         b) History of clinical response to oral cholinesterase inhibitors (for example: pyridostigmine)
         c) Electrophysiological evidence of abnormal neuromuscular transmission by repetitive nerve stimulation (RNS) or single-fiber electromyography (SFEMG)
   ii. Patients must NOT have a history of:
      1. Thymectomy within 12 months
      2. Current thymoma
      3. Other neoplasms of the thymus
   iii. Must have class II – IV disease
   iv. Previous treatment courses of at least 12 weeks with one of the following standards of care have been ineffective: methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, or tacrolimus unless all are contraindicated or not tolerated
   v. Patient is currently receiving, and will continue to receive, a stable standard of care regimen
   vi. Must not be using with other biologic therapies for myasthenia gravis or immunoglobulin therapy
e. Diagnosis of aquaporin-4 (AQP4) antibody positive neuromyelitis optica spectrum disorder (NMOSD)
   i. FDA approved age
   ii. Must not be used in combination with Uplizna™, Enspryng™, or other medications to treat neuromyelitis optica spectrum disorder (NMOSD)
   iii. Adequate trial and failure of an adequate trial of, contraindication, or intolerance to Uplizna, and Enspryng
f. Diagnosis of CHAPLE disease
   i. Confirmed biallelic CD55 loss-of-function mutation
   ii. Must not be used in combination with Veopoz™ or any other C5 complement inhibitor to treat CHAPLE disease
g. Coverage will be provided for biosimilar products for FDA labeled indications of the innovator product when criteria are met
h. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in WyoBlue Advantage's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***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.

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
1.0	Initial Effective Date: 01/01/2026	New policy

** 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.*