Health Partners Plans HPP

DR.006.C Complement Inhibitors: Eculizumab (Soliris®) & Ravulizumab (Ultomiris®)

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PRODUCT VARIATIONS

This policy applies to all Health Partners Plans (HPP) product lines unless noted below.

FDA INDICATIONS

- Eculizumab (Soliris®) was approved by the FDA on March 16, 2007, for treatment of paroxysmal nocturnal hemoglobinuria (PNH) in order to reduce hemolysis.
- Eculizumab (Soliris®) was approved by the FDA on September 23, 2011, for treatment of atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.
- Eculizumab (Soliris®) was approved by the FDA on October 23, 2017, for the treatment of adult individuals with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive.
- Eculizumab (Soliris®) was approved by the FDA on June 27, 2019 for the treatment of individuals with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.
- Ravulizumab (Ultomiris®) was approved by FDA on December 21, 2018 for the treatment of adults with Paroxysmal Nocturnal Hemoglobinuria (PNH).
- Ravulizumab (Ultomiris®) was approved by FDA on October 18, 2019 for the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).
- Ravulizumab (Ultomiris®) was approved by FDA on April 28, 2021 for the treatment of adults with Generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

POLICY STATEMENT

Initial use of Eculizumab (Soliris®) or Ravulizumab (Ultomiris®) may be considered medically necessary when **All** of the the following apply:

1) Vaccination for meningitis was completed at least 2 weeks prior to the start of therapy.

2) There is no evidence of serious systemic infections including Neisseria meningitides.

3) The prescriber is certified to prescribe the drug and is registered with the Soliris® and Ultomiris® Risk Evaluation Mitigation Strategy (REMS) Programs, available online at http://Solirisrems.com & http://www.utomirisrems.com.

4) Dosing is consistent with package label recommendations.

5) Member has ONE of the confirmed diagnoses listed below and criteria are met for that diagnosis.

   a. Paroxysmal Nocturnal Hemoglobinuria (PNH) and will receive Eculizumab (Soliris®) or Ravulizumab (Ultomiris®) to reduce hemolysis. **Initial approval up to 3 months.**

      ALL of the following must apply:

      i. Member is ≥ 18 years old.

      ii. Medication is prescribed by, or in consultation with a hematologist.

      iii. Diagnosis is confirmed by flow cytometry which demonstrates at least one of the following:

         (a) At least 10% PNH type III red cells OR

         (b) Greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP) - deficient polymorphonuclear cells (PMNs).

      iv. Member has biochemical evidence of hemolysis (measurement of serum concentration of lactate dehydrogenase (LDH), bilirubin (fractionated), and/or haptoglobin.

      v. Member has a history of at least one transfusion related to anemia secondary to PNH OR occurrence of a thromboembolic event.

   b. Atypical Hemolytic Uremic Syndrome (aHUS) and will receive Eculizumab (Soliris) or Ravulizumab (Ultomiris®) to inhibit complement-mediated thrombotic microangiopathy. **Initial approval up to 6 months.**

      All of the following must apply:

      i. Member is > 2 months old.

ii. Prescribed by, or in consultation with, a hematologist or nephrologist.

iii. Provider confirmed diagnosis of aHUS (including when diagnosed prior to end stage renal disease (ESRD) and when it recurs post-renal transplantation).

iv. Testing shows aHUS is not associated with Shiga Toxin E.coli.

v. Thrombotic Thrombocytopenic purpura has been ruled out (e.g., rule out ADAMTS13 deficiency).

c. Generalized Myasthenia Gravis and will receive Eculizumab or Ravulizumab (Ultomiris®)for treatment. Initial approval for 6 months.

ALL of the following must apply:

i. Anti-acetylcholine receptor (AchR) antibody positive and

ii. Refractory to standard treatments with immunosuppressant's- at least two (azathioprine; cyclosporine; mycophenolate mofetil; tacrolimus; methotrexate; cyclophosphamide) and

iii. Inadequate response to IVIG and rituximab and

iv. Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and

v. MG activities of daily living (MG-ADL) total score greater than or equal to 6; *and*

vi. Prescribed by or in consultation with neurologist

d. Neuromyelitis Optica Spectrum Disorder (NMOSD) and will receive Eculizumab (Soliris) for treatment. Initial approval 6 months. **ALL of the following apply:**

i. Individual is 18 years of age or older.

ii. Individual) is anti-aquaporin-4 (AQP4) antibody positive.

iii. Individual has failed treatment (for example, 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months) with: a corticosteroid (for example, prednisolone) and one other immunosuppressive agent (for example, azathioprine, cyclophosphamide, mycophenolate mofetil, rituximab).

iv. Eculizumab is prescribed by, or in, consultation with a neurologist.

v. Diagnosis of multiple sclerosis or other diagnoses have been ruled out.

Ongoing use of Eculizumab (Soliris®) and Ravulizumab (Ultomiris®); approval is up to 12 months) and may be considered medically necessary when **All** of the following apply:

1) The requested dose is consistent with the package label.
2) There are no serious adverse consequences/side effects of the drugs.
3) Vaccinations are current in accordance with ACIP guidelines.
4) Reassessment by the prescriber was done and shows:
    - **a. For PNH:**
        - i. Member requires fewer transfusions or has stabilization of Hb levels AND
        - ii. Reduction in intravascular hemolysis as evidenced reduction in markers of hemolysis.
    - **b. For aHUS:**
        - i. The initial criteria are met.
        - ii. Documented positive clinical response.

Ongoing use of Eculizumab (Soliris®); approval up to 12 months) for gMG with antibibodies.

i. The initial criteria are met.

ii. Documented positive clinical response (for example, reductions in exacerbations of MG; improvements in speech, swallowing, mobility, and respiratory function).

Ongoing use of Eculizumab (Soliris®).

Approval up to 12 months) for **Neuromyelitis Optica Spectrum Disorder** (NMOSD) when **All** of the following have been met:

i. The initial criteria are met.

ii. Documented positive clinical response (for example, reductions in relapse or reduction in new onset of symptoms).

Eculizumab (Soliris®) and Ravulizumab (Ultomiris®) are not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Use of Complement Inhibitors Eculizumab (Soliris®) and Ravulizumab (Ultomiris®) for other than the FDA approved indications are considered Experimental and Investigational and therefore is not covered by HPP.

OFF-LABEL USE

N/A.

PRIOR AUTHORIZATION CRITERIA

Prior authorization is required for Eculizumab (Soliris® and Ravulizumab (Ultomiris).

Treatment with Eculizumab (Soliris) and Ravulizumab (Ultomiris) is associated with life-threatening and fatal meningococcal infections. To mitigate this risk, a Risk Evaluation and Mitigation Strategy (REMS) have been developed. Health care providers are required to enroll in a registration program, certify that they will counsel and provide educational materials to patients about the risks of Eculizumab and Ravulizumab and agree to promptly report cases of meningococcal infection. The product labeling contains a boxed warning to inform healthcare providers and patients of the serious risk of meningococcal infection. The boxed warning recommends immunization with a polyvalent meningococcal vaccine.

Cautions:

- Patients are at an increased risk of meningococcal infections.
- Serious hemolysis may occur after interruption or discontinuation of therapy post PNH treatment.
- Thrombotic microangiopathy (TMA) complications may occur post aHUS treatment.
- Increased risk of systemic infections especially from encapsulated bacteria.

Monitoring:

- Serum LDH levels.
- Ferritin levels and symptoms of infusion reactions for at least one-hour post infusion.
- Early signs and symptoms of meningococcal infection.
- Early symptoms of hemolysis.
- Unresolved, serious Neisseria infection.
- Early signs of TMA with decrease in platelet count and increases in serum LDL and creatinine levels.

Pediatric Use:

- Use of Eculizumab (Soliris®) and Ravulizumab (Ultomiris) in paroxysmal nocturnal hemoglobinuria (PNH): The safety and effectiveness have not been established in the pediatric population.

- Use of Eculizumab (Soliris®) in atypical hemolytic uremic syndrome (aHUS): Four clinical studies assessing the safety and effectiveness of Eculizumab (Soliris®) for the treatment of aHUS included a total of 47 pediatric patients (ages 2 months to 17 years). The safety and effectiveness in the pediatric population is similar to that of the adult population.
- Use of Ravulizumab (Ultomiris) in atypical hemolytic uremic syndrome (aHUS): One open-label, single-arm trial 14 pediatric individuals. Initial benefit was assessed based on complete thrombotic microangiopathy (TMA) during a 26-week period as demonstrated by normalization of platelet count and lactate dehydrogenase, and at least 25% improvement in serum creatinine from baseline. Ravulizumab demonstrated a complete TMA response in 71% of individuals. (Ultomiris, 2019).
- Use of Eculizumab (Soliris®) and Ravulizumab (Ultomiris) in generalized Myasthenia Gravis (gMG): The safety and effectiveness have not been established in the pediatric population.

DOSAGE AND ADMINISTRATION

Eculizumab (Soliris®)			
BODY WEIGHT RANGE	MAX PER DOSE	MAX TOTAL FIRST 30 DAYS	MAX TOTAL PER 30 DAYS ONGOING
Greater than 40 kg	1200 mg	4800 mg	3600 mg
30-39 kg	900 mg	3000 mg	2700 mg
20-29 mg	600 mg	2400 mg	1800 mg
10-19 kg	600 mg	1200 mg	900 mg
Greater than 2 mo. Old & 5-9 kg	300 mg	900 mg	600 mg

Ravulizumab (Ultomiris) Weight-Based Dosing Regimen for PNH and gMB		
BODY WEIGHT RANGE (kg)	LOADING DOSE	MAINTENANCE DOSE
Greater than or equal to 40 to less than 60	2400 mg	3000 MG

Greater than or equal to 60 to less than 100	2700 mg	3300 MG
Greater than or equal to 100	3000 mg	3600 MG

Ravulizumab-cwvz (Ultomiris) Weight-Based Dosing Regimen for aHUS:		
BODY WEIGHT RANGE (kg)	LOADING DOSE	MAINTENANCE DOSE
Greater than or equal to 5 to less than 10	600 mg	300 MG (Every 4 weeks)
Greater than or equal to 10 to less than 20	600 mg	600 MG (Every 4 weeks)
Greater than or equal to 20 to less than 30	900 mg	2100 MG (Every 8 weeks)
Greater than or equal to 30 to less than 40	1200	2700 MG (Every 8 weeks)
Greater than or equal to 40 to less than 60	2400	3000 MG (Every 8 weeks)
Greater than or equal to 60 to less than 100	2700	3300 MG (Every 8 weeks)
Greater than or equal to 100	3000	3600 MG (Every 8 weeks)

Ravulizumab-cwvz (Ultomiris) Supplemental Dose; after PE, PP, or IVIg			
BODY WEIGHT RANGE (kg)	MOST RECENT UULTOMIRIS DOSE (mg)	SUPPLEMENTAL DOSE (mg) FOLLOWING EACH	SUPPLEMENTAL DOSE (mg) FOLLOWING COMPLETETION OF AN IVIg CYCLE

		PE OR PP INTERVENTION	
Greater than or equal to 40 to less than 60	2,400	1,200	600
	3,000	1,500	
Greater than or equal to 60 to less than 100	2,700	1,500	600
	3,300	1,800	
Greater than or equal to 100	3,000	1,500	600
	3,600	**1,800**	

Ravulizumab-cwvz (Ultomiris) On-Body Delivery System for Subcutaneous (SUBQ) Administration Treatment Initiation Instructions- Adults with PNH or aHUS		
Population	Weight – based Ultomiris®® IV loading dose	Time of first Ultomiris®490 mg SubQ Maintenance Dose
Not currently on Ultomiris® or eculizumab treatment.	At treatment start	2 weeks after Ultomiris® IV loading dose
Currently treated with eculizumanb.	At time of next scheduled eculizumab dose	2 weeks after Ultomiris® IV loading dose
Currently treated with Ultomiris® IV administration	Not applicable	8 weeks after last Ultomiris® IV maintenance dose

The recommended dosing regimen in adult and pediatric persons 1 month of age and older with aHUS weighing 5 kg or greater, consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. Administer the doses based on the person's body weight, as shown in the table. Starting 2 weeks after the loading dose administration, begin maintenance doses once every 8 weeks or every 4 weeks (depending on body weight). GE AND ADMINISTRATION

BENEFIT APPLICATION

Medical policies do not constitute a description of benefits. This medical necessity policy assists in the administration of the member's benefits which may vary by line of business. Applicable benefit documents govern which services/items are eligible for coverage, subject to benefit limits, or excluded completely from coverage.

This policy is invoked only when the requested service is an eligible benefit as defined in the Member's applicable benefit contract on the date the service was rendered. Services determined by the Plan to be investigational or experimental are excluded from coverage for all lines of business. For Medicaid members under 21 years old, benefits and coverage are always based on medical necessity review.

DESCRIPTION OF SERVICES

On September 23, 2011, the U.S. Food and Drug Administration (FDA) granted accelerated approval for the use of Eculizumab (Soliris®, Alexion, Inc.) for the treatment of pediatric and adult patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

On December 21, 2018, the U.S. Food and Drug Administration (FDA) granted accelerated approval for the use of Ravulizumab (Ultomiris, Alexion, Inc.) for the treatment of adults with Paroxysmal Nocturnal Hemoglobinuria (PNH).

Eculizumab (Soliris®) and Ravulizumab (Ultomiris®) are monoclonal antibodies that inhibit the production of the terminal complement components C5a, and the membrane attack complex C5b-9 by binding to complement protein C5. Prevention of the formation of C5a and the terminal complement complex inhibits complement-mediated thrombotic microangiopathy in patients with aHUS. Eculizumab and Ravulizumab are approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

Eculizumab (Soliris®) and Ravulizumab (Ultomiris) are not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, potentially life-threatening disease of the blood characterized by complement-induced hemolytic anemia (anemia due to destruction of red blood cells in the bloodstream), red urine (due to the appearance of hemoglobin in the urine) and thrombosis. PNH is the only hemolytic anemia caused by an acquired (rather than inherited) intrinsic defect in the cell membrane (deficiency of glycophosphatidylinositol leading to absence of protective proteins on the membrane). It may develop on its own ("primary PNH") or in the context of other bone marrow disorders such as aplastic anemia ("secondary PNH"). Ham test and sucrose hemolysis can be done to diagnose paroxysmal nocturnal hemoglobinuria (PNH). A positive test can confirm the diagnosis of PNH. These tests can be falsely negative if you have received recent red blood cell transfusions. Therefore, over the past several years flow cytometry has become the gold standard for diagnosis.[1]

Atypical hemolytic-uremic syndrome (aHUS) is a disease that primarily affects the kidneys. This condition, which can occur at any age, causes abnormal blood clots to form in the small blood vessels of the kidneys. Atypical hemolytic-uremic syndrome is characterized by three major features related to abnormal clotting: hemolytic anemia, thrombocytopenia, and kidney failure. As a result of clot formation, people with atypical hemolytic-uremic syndrome experience kidney damage and acute

kidney failure that led to end-stage renal disease (ESRD) in about half of all cases. These life-threatening complications prevent the kidneys from functioning properly. Atypical hemolytic-uremic syndrome often results from a combination of environmental and genetic factors. The incidence of atypical hemolytic-uremic syndrome is estimated to be 1/500,000 people per year in the US. The atypical form is probably about 10 times less common than the typical form. [2]

On October 23, 2017, Alexion Pharmaceuticals, Inc., announced that the U.S. Food and Drug Administration (FDA) approved Soliris® (Eculizumab) as a treatment for adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive. In the Phase 3 REGAIN study and its ongoing open-label extension study, Soliris® demonstrated treatment benefits for patients with anti-AchR antibody-positive gMG who had previously failed immunosuppressive treatment and continued to suffer from significant unresolved disease symptoms, which can include difficulties seeing, walking, talking, swallowing, and breathing. These patients are at an increased risk of disease exacerbations and crises that may require hospitalization and intensive care and may be life-threatening. These patients represent approximately 5-10% of all patients with MG.

On June 27, 2019, Alexion Pharmaceuticals, Inc., announced that the U.S. Food and Drug Administration (FDA) approved Soliris® (Eculizumab) as a treatment for adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare and debilitating autoimmune disease of the central nervous system (CNS), characterized by inflammation in the optic nerve and spinal cord. NMOSD optic neuritis attacks cause eye pain and vision loss. Attacks can also result in numbness, weakness, or paralysis of the arms and legs, along with loss of bladder and bowel control.

CLINICAL EVIDENCE

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

PNH is a rare condition caused by genetic mutation in the production of red blood cells (RBCs). The mutation causes red blood cells (RBCs) to form without terminal complement inhibitors. The absence of complement inhibitors leads to the constant premature destruction and loss of RBCs (hemolysis) by the individual's own immune system. The premature loss of RBCs can result in anemia, fatigue, difficulty in functioning, dark urine, pain, shortness of breath, and blood clots. Eculizumab (Soliris®) inhibits RBC mutation and prevents intravascular hemolysis.

The safety and efficacy of Eculizumab (Soliris®) in individuals with PNH with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26-week study (Study 1); individuals with PNH were also treated with Eculizumab (Soliris®) in a single arm 52-week study (Study 2); and in a long-term extension study. Individuals received meningococcal vaccination prior to receipt of Eculizumab (Soliris®). In all studies, the dose of Eculizumab (Soliris®) was 600 mg every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Eculizumab (Soliris®) was administered as an intravenous infusion over 25 to 45 minutes.

In Study 1, individuals with PNH with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either Eculizumab (Soliris®) (n=43) or placebo (n=44). Prior to randomization, all individuals underwent an initial observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point") which would define each individual's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in individuals with symptoms and was less than or equal to 7 g/dL in individuals without symptoms. Endpoints related to hemolysis included the numbers of individuals achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, an individual had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26-week period. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Individuals receiving anticoagulants and systemic corticosteroids at baseline continued these medications. Individuals treated with Eculizumab (Soliris®) had significantly reduced ($p< 0.001$) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to individuals receiving placebo. These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 to 14 units; 15 to 25 units; > 25 units). After three weeks of Eculizumab (Soliris®) treatment, individuals reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of Eculizumab (Soliris®) on thrombotic events could not be determined.

In Study 2 and the long-term extension study, individuals with PNH with at least one transfusion in the prior 24 months and a platelet count of at least 30,000 platelets/microliter received Eculizumab (Soliris®) over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the individuals and systemic corticosteroids in 40% of the individuals. Overall, 96 of the 97 enrolled individuals completed the study (one individual died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. 187 individuals treated with Eculizumab (Soliris®) were enrolled in a long-term extension study. All individuals sustained a reduction in intravascular hemolysis over a total Eculizumab (Soliris®) exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Eculizumab (Soliris®) treatment than during the same period prior to treatment. However, the majority of individuals received concomitant anticoagulants; the effect of anticoagulant withdrawal during Eculizumab (Soliris®) therapy was not studied.

Safety and efficacy of Ravulizumab were evaluated in two phase 3 trials that demonstrated non-inferiority of Ultomiris to Eculizumab in both treatment-naïve individuals and those who received prior therapy with Soliris. In CHAMPION-301, complement inhibitor-naïve adults were randomized to receive weight-based Ravulizumab or Eculizumab for 26 weeks. Individuals assigned to Ravulizumab received a loading dose followed by maintenance dosing every 8 weeks, while those assigned to Eculizumab received a dose on days 1, 8, 15, and 22 followed by maintenance dosing on day 29 and every 2 weeks. Benefit was assessed based on coprimary endpoints; the first was the proportion of individuals remaining transfusion-free, and the second, reduction of hemolysis as measured by normalization of lactate dehydrogenase (LDH) levels. Transfusion avoidance seen in about 74% and about 66% of individuals who received Ravulizumab and eculizumab, respectively.

In CHAMPION-302, individuals receiving eculizumab for at least six months were randomized to switch treatment to Ravulizumab or continue eculizumab. Benefit was assessed based on hemolysis as measured by LDH percent change from baseline to day 183. Ravulizumab demonstrated noninferiority compared with eculizumab in the primary endpoint.

ATYPICAL HEMOLYTIC-UREMIC SYNDROME (aHUS)

Atypical hemolytic-uremic syndrome (aHUS) is a rare and chronic blood disease that primarily affects kidney function. This condition can occur at any age but disproportionately affects children. The syndrome causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. aHUS are characterized by three major features related to abnormal clotting: hemolytic anemia, thrombocytopenia, and kidney failure. Studies revealed that eculizumab (Soliris®) was effective in improving kidney function and platelet count in pediatric and adult individuals, and in some cases eliminated the need for dialysis.

Five single-arm studies [four prospective (aHUS Studies 1, 2, 4 and 5) and one retrospective (aHUS Study 3)] evaluated the safety and efficacy of eculizumab (Soliris®) for the treatment of aHUS. Individuals with aHUS received meningococcal vaccination prior to receipt of eculizumab (Soliris®) or received prophylactic treatment with antibiotics until two weeks after vaccination. In all studies, the dose of eculizumab (Soliris®) in adults and adolescents was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg 7 ± 2 days later, then 1200 mg every 14 ± 2 days thereafter. The dosage regimen for pediatric individuals weighing less than 40 kg enrolled in aHUS study 3 and study 5 was based on body weight. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints. Endpoints related to TMA included the following:

- Platelet count change from baseline.
- Hematologic normalization (maintenance of normal platelet counts and LDH levels for at least four weeks).
- Complete TMA response (hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks).
- TMA-event free status (absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement).
- Daily TMA intervention rate (defined as the number of plasma exchange or plasma infusion interventions and the number of new dialyses required per individual per day).

aHUS Study 1 enrolled individuals who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four plasma exchange/plasma infusion (PE/PI) treatments the week prior to screening. One individual had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, individuals were required to have a platelet count ≤150 x 109 /L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median age was 28 (range: 17 to 68 years). Individuals enrolled in aHUS Study 1 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 70% to 121%. Seventy-six

percent of individuals had an identified complement regulatory factor mutation or auto-antibody. Individuals in aHUS Study 1 received Eculizumab (Soliris®) for a minimum of 26 weeks. In aHUS Study 1, the median duration of Eculizumab (Soliris®) therapy was approximately 100 weeks (range: 2 weeks to 145 weeks). Renal function, as measured by eGFR, was improved, and maintained during Eculizumab (Soliris®) therapy. The mean eGFR (± SD) increased from 23 ± 15 mL/min/1.73m^2 at baseline to 56 ± 40 mL/min/1.73m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73m^2). Four of the five individuals who required dialysis at baseline were able to discontinue dialysis. Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Eculizumab (Soliris®). Eculizumab (Soliris®) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS Study 1, mean platelet count (± SD) increased from 109 ± 32 x109 /L at baseline to 169 ± 72 x109 /L by one week; this effect was maintained through 26 weeks (210 ± 68 x109 /L), and 2 years (205 ± 46 x109 /L). When treatment was continued for more than 26 weeks, two additional individuals achieved hematologic normalization as well as complete TMA response. Hematologic normalization and complete TMA response were maintained by all responders. In aHUS Study 1, responses to Eculizumab (Soliris®) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins.

aHUS Study 2 enrolled individuals undergoing chronic PE/PI who generally did not display hematologic signs of ongoing thrombotic microangiopathy (TMA). All individuals had received PT at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first Eculizumab (Soliris®) dose. Individuals on chronic dialysis were permitted to enroll in aHUS Study 2. The median age was 28 years (range: 13 to 63 years). Individuals enrolled in aHUS Study 2 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 37% to 118%. Seventy percent of individuals had an identified complement regulatory factor mutation or auto-antibody. Individuals in aHUS Study 2 received Eculizumab (Soliris®) for a minimum of 26 weeks. In aHUS Study 2, the median duration of Eculizumab (Soliris®) therapy was approximately 114 weeks (range: 26 to 129 weeks). Renal function, as measured by eGFR, was maintained during Eculizumab (Soliris®) therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m^2 at baseline and was maintained through 26 weeks (37 ± 21 mL/min/1.73m^2) and two years (40 ± 18 mL/min/1.73m^2). No individual required new dialysis with Eculizumab (Soliris®). Reduction in terminal complement activity was observed in all individuals after the commencement of Eculizumab (Soliris®). Eculizumab (Soliris®) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 x 109 /L at baseline, 233 ± 69 x 109 /L at week 26, and 224 ± 52 x 109 /L at two years. When treatment was continued for more than 26 weeks, six additional individuals achieved complete TMA response. Complete TMA response and hematologic normalization were maintained by all responders. In aHUS Study 2, responses to Eculizumab (Soliris®) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins.

The efficacy results for the aHUS retrospective study (aHUS Study 3) were generally consistent with results of the two prospective studies. Eculizumab (Soliris®) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 x109 /L at baseline to 233 ±109 x109 /L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count (± SD) at

week 26: 254 ± 79 x109 /L). A total of 19 pediatric individuals (ages 2 months to 17 years) received Eculizumab (Soliris®) in aHUS Study 3. The median duration of Eculizumab (Soliris®) therapy was 16 weeks (range 4 to 70 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for individuals 12 to <18 years of age (n=4). Fifty three percent of pediatric individuals had an identified complement regulatory factor mutation or auto-antibody. Overall, the efficacy results for these pediatric individuals appeared consistent with what was observed in individuals enrolled in aHUS Studies 1 and 2. No pediatric individuals required new dialysis during treatment with Eculizumab (Soliris®).

aHUS Study 4 enrolled individuals who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrollment, individuals were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median age was 35 (range: 18 to 80 years). All individuals enrolled in aHUS Study 4 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28%-116%. Fifty-one percent of individuals had an identified complement regulatory factor mutation or auto-antibody. A total of 35 individuals received PE/PI prior to Eculizumab (Soliris®). Individuals in aHUS Study 4 received Eculizumab (Soliris®) for a minimum of 26 weeks. In aHUS Study 4, the median duration of Eculizumab (Soliris®) therapy was approximately 50 weeks (range: 13 weeks to 86 weeks). Renal function, as measured by eGFR, was improved during Eculizumab (Soliris®) therapy. The mean eGFR (± SD) increased from 17 ± 12 mL/min/1.73m^2 at baseline to 47 ± 24 mL/min/1.73m^2 by 26 weeks. Twenty of the 24 individuals who required dialysis at study baseline were able to discontinue dialysis during Eculizumab (Soliris®) treatment. Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Eculizumab (Soliris®). Eculizumab (Soliris®) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS Study 4, mean platelet count (± SD) increased from 119 ± 66 x109 /L at baseline to 200 ± 84 x109 /L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 252 ± 70 x109 /L). In aHUS Study 4, responses to Eculizumab (Soliris®) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

aHUS Study 5 enrolled individuals who were required to have a platelet count < LLN, evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥ 97 percentile for age without the need for chronic dialysis. The median age was 6.5 (range: 5 months to 17 years). Individuals enrolled in aHUS Study 5 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of individuals had an identified complement regulatory factor mutation or auto-antibody. A total of 10 individuals received PE/PI prior to Eculizumab (Soliris®). Individuals in aHUS Study 5 received Eculizumab (Soliris®) for a minimum of 26 weeks. In aHUS Study 5, the median duration of Eculizumab (Soliris®) therapy was approximately 44 weeks (range: 1 dose to 88 weeks). Renal function, as measured by eGFR, was improved during Eculizumab (Soliris®) therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73m^2 at baseline to 98 ± 44 mL/min/1.73m^2 by 26 weeks. Among the 20 individuals with a CKD stage ≥ 2 at baseline, 17 (85%) achieved a CKD improvement of ≥1 stage. Among the 16 individuals ages 1 month to <12 years with a CKD stage ≥ 2 at baseline, 14 (88%) achieved a CKD improvement by ≥ 1 stage. Nine of the 11 individuals who required daily dialysis at study baseline were able to discontinue dialysis during Eculizumab (Soliris®) treatment. Responses were observed across all ages from 5

months to 17 years of age. Reduction in terminal compliment activity was observed in all individuals after commencement with Eculizumab (Soliris®). Eculizumab (Soliris®) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ± 42 x109 /L at baseline to 281 ± 123 x109 /L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 x109 /L). In aHUS Study 5, responses to Eculizumab (Soliris®) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Clinical experience with Ravulizumab is based on two open-labels, single-arm trials. 56 adult individuals were assessed for efficacy in trial 1 and 14 pediatric individuals in trial 2. Initial benefit was assessed based on complete thrombotic microangiopathy (TMA) during a 26-week period as demonstrated by normalization of platelet count and lactate dehydrogenase, and at least 25% improvement in serum creatinine from baseline. In trial 1, Ravulizumab demonstrated a complete TMA response in 54% of individuals. In trial 2, Ravulizumab demonstrated a complete TMA response in 71% of individuals. (Ultomiris, 2019)

GENERALIZED MYASTHENIA GRAVIS

Myasthenia Gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles. The muscle weakness usually worsens after periods of activity and improves after periods of rest. Muscles that control movements of the eye and eyelid, facial expression, chewing, talking, and swallowing are often involved, but those that control breathing and neck and limb movements may also be involved. This weakness is a result of an antibody-mediated, T-cell dependent, immunological attack directed at proteins in the postsynaptic membrane of the neuromuscular junction. Myasthenia Gravis has an annual incidence of about 7 to 23 cases per million. It most often begins before the age of 40 in women and after age 60 in men.

The efficacy of eculizumab (Soliris®) for the treatment of generalized myasthenia gravis was established in a 26 week, randomized, double-blind, placebo-controlled, parallel group, multicenter trial (REGAIN) in 125 individuals. Among the inclusion criteria for this trial were a positive serologic test for anti-acetylcholine receptor (AChR) antibodies, MG-Activities of daily living (MG-ADL) score ≥ 6, and failed treatment over 1 year or more with 2 or more immunosuppressive therapies or failed 1 immunosuppressive treatment and required chronic plasma exchange or IVIG. The primary endpoint of this trial was a change from baseline in the Myasthenia Gravis Activities of daily living scale total score at week 26 between the placebo group and the eculizumab (Soliris®) group. The Myasthenia Gravis-activities of daily living scale is a patient-reported scale developed to assess 8 typical signs and symptoms of MG and their effects on daily activities. Each item is assessed on a 4-point scale where 0 is normal function and 3 indicates loss of ability to perform that function. The change in MG-ADL score in the eculizumab (Soliris®) treated group was -4.2 versus -2.3 in the placebo group. This trial narrowly missed statistical significance for the primary endpoint (p=0.0698), however, 18 of 22 pre-specified endpoints and analyses, based on the primary and five secondary endpoints, had results with p-values<0.05 across the four assessment scales. A secondary endpoint was the change in Quantitative Myasthenia Gravis score. This is a 13-item, 4-point categorical scale assessing muscle weakness from 0, representing no weakness, to 3 which represents severe weakness. a statistically significant different was observed in the mean change from baseline to

week 26, in favor of Soliris®, in total QMG scores (-4.6 in Soliris® group versus -1.6 in placebo group).

CODING

Note*:* The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that *may* be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

CPT® is a registered trademark of the American Medical Association.

CPT Code	Description
N/A	N/A

HCPCS Code	Description
J1300	Injection, Eculizumab, 10 mg
J1303	Injection, Ravulizumab, 10mg

ICD-10 Codes	Description
D59.3	Hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
G36.0	Neuromyelitis optica [Devic]
G70.0	Myasthenia Gravis
G70.00	Myasthenia Gravis without acute exacerbation
G70.01	Myasthenia Gravis with acute exacerbation

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making.

Policy Bulletins are developed by Health Partners Plans (HPP) to assist in administering plan benefits and constitute neither offers of coverage nor medical advice.

This Policy Bulletin may be updated and therefore is subject to change.

For HealthChoices (Medicaid) and Children's Health Insurance Program (CHIP) products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
Policy updated due to new FDA labeling.	C	12/1/2022
Annual review. Policy statement revised for clarity.	B	4/1/2022
Annual review. No changes for 2021.	A	7/1/2020
New policy.	A	7/1/2020

REFERENCES

1. Soliris® [package insert]. Cheshire, CT: Alexion Pharmaceuticals, Inc..
2. Hillmen P, Muus P, Duhrsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood.* 2007;110:4123-4128.
3. Rosse WF. A new way to prevent thrombosis? *Blood*. 2007; 110: 3821.
4. Höchsmann, B., Rojewski, M. & Schrezenmeier, H. Ann Hematol (2011) 90: 887. https://doi.org/10.1007/s00277-011-1177-4
5. Borowitz MJ, Craig FE, Diguiseppe JA, et al; on behalf of the Clinical Cytometry Society. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry B Clin Cytom. 2010;78:211-230.
6. Takeda J, Miyata T, Kawagoe K, et al. Deficiency of the GPI anchor caused by somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. Cell. 1993;73:703-711.

7. Parker C, Omine M, Richards S, et al; and the International PNH Interest Group. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005;12:3699-3709.
8. Hillmen P, Lewis SM, Bessler M, et al. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995;333:1253-1258.
9. Hillmen P, Hall C, Marsh JCW, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2004;350:552-559.
10. Hall C, Richards S, Hillmen P. Primary prophylaxis with warfarin prevents thrombosis in paroxysmal nocturnal hemoglobinuria (PNH). Blood. 2003;102:3587-3591.
11. Parker C, Management of Paroxysmal Nocturnal Hemoglobinuria in the Era of Complement Inhibitor Therapy, Hematology, 2011, 1: 21-29 http://asheducationbook.hematologylibrary.org/content/2011/1/21.full
12. Salvadori M, Bertoni E. Update on hemolytic uremic syndrome: Diagnostic and therapeutic recommendations. World Journal of Nephrology. 2013;2(3):56-76. doi:10.5527/wjn.v2.i3.56.
13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3832913/#
14. Nester, C, Thomas . Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated. Hematology, 2012, 1: 617-625. Available at http://asheducationbook.hematologylibrary.org/content/2012/1/617.full
15. OneSource™ Safety Support. Available at http://www.Soliris®rems.com.
16. Hillmen P, Muus P, Röth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2013 Apr 25. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3744747/.
17. Noris M, Bresin E, Mele C, Remuzzi G. Genetic Atypical Hemolytic-Uremic Syndrome.
18. GeneReviews® [Internet]. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1367/.
19. Schrezenmeier H, Muus P, Socié G, Szer J, Urbano-Ispizua A, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica. 2014 May; 99(5):922-9. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4008114/.
20. Canadian Agency for Drugs and Technologies in Health (CADTH). Eculizumab. (Soliris® – Alexion Pharmaceuticals, Inc.). Indication: Paroxysmal nocturnal hemoglobinuria. CEDAC Final Recommendation. Common Drug Review. Ottawa, ON: CADTH; February 19, 2010. Available at https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Soliris®_February_18_2010.pdf.
21. Robert A. Brodsky, Neal S. Young, Elisabetta Antonioli, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood, 15 February 2008. Volume 111, Number 4. Available at http://www.bloodjournal.org/content/bloodjournal/111/4/1840.full.pdf.
22. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome. N Engl J Med 2013; 368:2169-81. Available at http://www.nejm.org/doi/pdf/10.1056/NEJMoa1208981
23. Brodsky, RA. Clinical Manifestations and Diagnosis of Paroxysmal Nocturnal Hemoglobinuria. UpToDate. Updated 10/08/2019.

24. Brodsky, RA. Treatment and Prognosis of Paroxysmal Nocturnal Hemoglobinuria.pToDate. Updated 01/09/2019.
25. Niaudet, P. Complement –mediated hemolytic uremic syndrome in children. UpToDate. Updated 07/24/2019
26. Lapeyraque AL, Malina M, Fremeaux-Bacchi V, et al. Eculizumab in Severe Shiga-Toxin-Associated HUS. N Engl J Med. 2011 Jun 30; 364(26):2561-3. Available at http://www.nejm.org/doi/full/10.1056/NEJMc1100859.
27. McEvoy GK, Pharm.D., ed. 2019. AHFS Drug Information® - 59th Ed. Bethesda, MD. American Society of Health-System Pharmacists.
28. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Publication last updated: May 2017. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-FactSheet. Accessed on June 4, 2019.
29. Pittock SJ, Lennon VA, McKeon A, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. Lancet Neurol Apr 26 2013; 12:554-62.
30. Sadaka B, Alloway RR, Woodle ES. Management of antibody-mediated rejection in transplantation. Surgical Clinics of North America 2013; 93(6):1451-66.
31. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016 Jul 26;87(4):419-25.
32. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol. 2010 Aug;17(8):1019-32.
33. Soliris® injection [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; June 2019.
34. Ultomiris® injection [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; August 2022.