DR.006.G Complement Inhibitors: Eculizumab & Ravulizumab

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PRODUCT VARIATIONS

This policy applies to all Jefferson Health Plans/Health Partners Plans lines of business unless noted below.

POLICY STATEMENT

We consider Compliment Inhibitors: Eculizumab (Soliris®), Eculizumab-aagh (EPYSQLI®), Eculizumab-aeeb (BKEMV®), Ravulizumab (Ultomiris®), and any new biosimilars covered and medically necessary when all of the prior authorization criteria listed in this policy are met.

FDA INDICATIONS

- Eculizumab (Soliris®) was approved by the FDA on March 16, 2007, for treatment of paroxysmal nocturnal hemoglobinuria (PNH) 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 for the treatment of adult and pediatric patients six years of age and older 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.

- Eculizumab-aagh (EPYSQLI®) was approved by FDA on July 22, 2024, for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Eculizumab-aagh (EPYSQLI®) is biosimilar to Eculizumab (Soliris®).

    - Limitation of Use: EPYSQLI® is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.

- Eculizumab-aeeb (BKEMV®) was approved by FDA on May 28, 2024, for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Eculizumab-aeeb (BKEMV®) is biosimilar to Eculizumab (Soliris®).

    - Limitation of Use: BKEMV® is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) 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 June 7, 2021, for the children and adolescents with Paroxysmal Nocturnal Hemoglobinuria (PNH).

- Ravulizumab (Ultomiris®) was approved by FDA on April 28, 2022, for the treatment of adults with Generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

- Ravulizumab (Ultomiris®) was approved by FDA on March 25, 2024, for the treatment of adults with Neuromyelitis Optica Spectrum Disorder (NMOSD).

PRIOR AUTHORIZATION CRITERIA

Initial use of Eculizumab (Soliris®), Eculizumab-aeeb (BKEMV®), Eculizumab-aagh (EPYSQLI®), or Ravulizumab (Ultomiris®) may be considered medically necessary when **All** of the following apply:

1. Is being treated for a diagnosis that is indicated in the U.S. FDA-approved package insert OR is medically accepted indication; **AND**
2. Vaccination for meningitis was completed at least 2 weeks prior to the start of therapy; **AND**
3. There is no evidence of serious systemic infections, including *Neisseria meningitides;* **AND**
4. The Complement Inhibitor is prescribed by or in consultation with an appropriate specialist (i.e. hematologist/oncologist, nephrologist, neurologist); **AND**
5. The prescriber is certified to prescribe the drug and is registered with the Soliris®, BKEMV®, EPYSQLI® and Ultomiris® Risk Evaluation Mitigation Strategy (REMS) Programs, available online at:
    a. ULTOMIRIS and SOLIRIS REMS - Home
    b. BKEMV REMS | eculizumab - Home
    c. Epysqli REMS Healthcare Setting and Pharmacy

6. Is prescribed at a dose that is consistent with FDA-approved package label recommendations, nationally recognized compendia, or peer-reviewed; **AND**
7. 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®), Eculizumab-aeeb (BKEMV®), Eculizumab-aagh (EPYSQLI®), or Ravulizumab (Ultomiris®) to reduce hemolysis. **Initial approval up to 3 months.**

    ALL the following must apply:

    - Member is ≥ 18 years old for Soliris® OR ≥ 1 month old for Ultomiris®.
    - Medication is prescribed by, or in consultation with a hematologist.
    - Diagnosis is confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) which demonstrates at least one of the following:
        - At least 5% PNH type III red cells OR-
        - Greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP) - deficient polymorphonuclear cells (PMNs).
    - Flow cytometry is used to demonstrate GPI-anchored proteins deficiency.
    - Member has biochemical evidence of hemolysis (measurement of serum concentration of lactate dehydrogenase (LDH), bilirubin (fractionated), and/or haptoglobin.
    - 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), Eculizumab-aeeb (BKEMV®), Eculizumab-aagh (EPYSQLI®), or Ravulizumab (Ultomiris®) to inhibit complement-mediated thrombotic microangiopathy. **Initial approval up to 6 months.**

All of the following must apply:

- Member is ≥ 18 years old for Soliris® OR ≥ 1 month old for Ultomiris®
- Prescribed by, or in consultation with, a hematologist or nephrologist.
- Provider confirmed diagnosis of aHUS (including when diagnosed prior to end stage renal disease (ESRD) and when it recurs post-renal transplantation).
- Testing shows aHUS is not associated with Shiga Toxin E. coli.
- Thrombotic Thrombocytopenic purpura has been ruled out (e.g., rule out ADAMTS13 activity level above 5%).

C. Generalized Myasthenia Gravis and will receive Eculizumab (Soliris®), Eculizumab-aeeb (BKEMV®), Eculizumab-aagh (EPYSQLI®), or Ravulizumab (Ultomiris®) for treatment. Initial approval for 6 months.

All of the following must apply:

- Anti-acetylcholine receptor (AchR) antibody positive and
- Refractory to standard treatments with immunosuppressant's or intolerable adverse event to at least two immune suppressive therapies over the course of 12 months (azathioprine; cyclosporine; mycophenolate mofetil; tacrolimus; methotrexate; cyclophosphamide) and one of the following:
    - Member has had an inadequate response or intolerable adverse event to at least one immunosuppressive therapy and intravenous immunoglobulin (IVIG) over the course of at least 12 months
    - Member has a documented clinical reason to avoid therapy with immunosuppressive agents and IVIG
- The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris, Soliris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo.)
- Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and

- MG activities of daily living (MG-ADL) total score greater than or equal to 5; and
- Prescribed by or in consultation with neurologist.

D. Neuromyelitis Optica Spectrum Disorder (NMOSD) and will receive Eculizumab (Soliris®) or Ravulizumab (Ultomiris®) for treatment. Initial approval 6 months.

All of the following must apply:

- Individual is 18 years of age or older.
- Individual is anti-aquaporin-4 (AQP4) antibody positive.
- Individual has documentation of one of the following clinical characteristics:
  - Optic neuritis
  - Acute myelitis
  - Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
  - Acute brainstem syndrome
  - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
  - Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- Prescribed by, or in, consultation with a neurologist.
- Diagnosis of multiple sclerosis or other diagnoses have been ruled out.
- Individual will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Ongoing use of Eculizumab (Soliris®), Eculizumab-aeeb (BKEMV®), Eculizumab-aagh (EPYSQLI®), 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. No evidence of unacceptable toxicity or disease progression

5. Reassessment by the prescriber was done and shows:
    - **For PNH:**
        - Documented positive clinical response such as: needing fewer transfusions, stabilization of Hb levels, normalization of lactate dehydrogenase [LDH] levels normalization of lactate dehydrogenase [LDH] levels.
    - **For aHUS:**
        - Documented positive clinical response such as improvement in hemoglobin levels, normalization of LDH levels.
    - **For gMG with antibodies** when **All** of the following have been met:
        - The initial criteria are met.
        - Documented positive clinical response (for example, reductions in exacerbations of MG; improvements in speech, swallowing, mobility, and respiratory function; improvement in MG-ADL score, MG Manual Muscle Test [MMT], MG Composite).
        - The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris, Soliris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystigg
    - **Neuromyelitis Optica Spectrum Disorder (NMOSD**) when **All** of the following have been met:
        - Documented positive clinical response (for example, reductions in relapse or reduction in new onset of symptoms).
        - Individual will not receive requested medication concomitantly with other biologics for the treatment of NMOSD.

Eculizumab (Soliris®), Eculizumab-aagh (EPYSQLI®), Eculizumab-aeeb (BKEMV®), and Ravulizumab (Ultomiris®) are contraindicated for initiation in patients with unresolved serious *Neisseria meningitidis* infection.

OFF-LABEL USE

Complement Inhibitors Eculizumab (Soliris®), Eculizumab-aagh (EPYSQLI®), Eculizumab-aeeb (BKEMV®), and Ravulizumab (Ultomiris®) for other than the FDA approved indications are considered Experimental and Investigational and therefore is not covered.

BLACK BOX WARNING

Treatment with Eculizumab (Soliris®), Eculizumab-aagh (EPYSQLI®), Eculizumab-aeeb (BKEMV®), and Ravulizumab (Ultomiris®) is associated with life-threatening and fatal meningococcal infections. To mitigate this risk, a Risk Evaluation and Mitigation Strategy (REMS) has been developed. Healthcare settings and pharmacies that dispenses Soliris must be certified in REMS. 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 complete or update immunization at least 2 weeks with a polyvalent meningococcal vaccine (serogroups A, C, W, Y and B) prior to receiving a complement inhibitor. Providers must provide prophylaxis antimicrobial treatment, if treatment with a complement inhibitor must be started urgently and the patient is not up to date or vaccinated with meningococcal vaccines. Patients are informed to always carry a Patient Safety Card during and 3 months post treatment.

Cautions:

- Serious 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.
- Use caution when administering to patients with any other systemic infection.

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.
- *N. meningitidis*: Patients are at increased risk for invasive disease caused by N. meningitidis, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of meningococcal infections and evaluate immediately if infection is suspected.

- Infusion-related reactions: monitor patients during infusion, interrupt for reactions, and institute appropriate supportive measures.

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 Ravulizumab (Ultomiris®) in generalized Myasthenia Gravis (gMG): The safety and effectiveness have not been established in the pediatric population.
- Use of Eculizumab-aeeb (BKEMV®) and Eculizumab-aagh (EPYSQLI®) for treatment of PNH and gMG in pediatric patients: safety and efficacy have not been established.
- Use of Eculizumab-aeeb (BKEMV®) and Eculizumab-aagh (EPYSQLI®) for treatment of aHUS in pediatric patients: safety and efficacy have been established.

DOSAGE AND ADMINISTRATION

Eculizumab (Soliris®)

Administration:

- Eculizumab (Soliris®) is available as 300 mg/ 30 mL (10 mg/mL) single-dose vial.
- Only administer as an intravenous infusion, do not administer as an intravenous push or bolus injection.
- Administer as an infusion over 35 minutes for adults, and 1-4 hours for pediatric patients through a gravity feed, syringe type pump, or infusion pump.
- Solutions are stable for 24 hours at room temperature.
- In an event of an adverse reaction during administration of Soliris, the infusion may be decreased or stopped. If the infusion is decreased the total infusion time should not exceed 2 hours in adults.
- Monitor patient for a minimum of 1 hour if there are signs or symptoms of an infusion reaction.

Eculizumab (Soliris®) recommended dosage regimen for PNH (18 years and older)	
DOSE	DOSING INTERVAL
600 mg weekly (4 doses total)	Weekly for first 4 weeks
900 mg (5th dose)	Week 5 (after first 4 weeks)
900 mg	Every 2 weeks there after

Eculizumab (Soliris®) Recommended dosage regimen for aHUS, gMG & NMOSD (18 years and older)	
DOSE	DOSING INTERVAL
900 mg weekly (4 doses total)	Weekly for the first 4 weeks
1200 mg (5th dose)	Week 5 (after first 4 weeks)
1200 mg	Every 2 weeks there after

Eculizumab (Soliris®) Recommended dosage regimen for aHUS (Less than 18 years)		
Patient Body Weight	**Induction**	**Maintenance**
40 kg and over	900 mg weekly for the first 4 weeks	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg for the first 2 weeks	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg for the first 2 weeks	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg single dose at Week 1	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg single dose at Week 1	300 mg at week 2; then 300 mg every 3 weeks

Eculizumab (Soliris®) Supplemental Dose after Plasmapheresis, Plasma Exchange, Fresh Frozen Plasma Infusion			
Type of Plasma Intervention	**Most Recent Soliris® Dose**	**Supplemental Soliris® Dose with Each Plasma Intervention**	**Timing of Supplemental Soliris® Dose**
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange

	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Eculizumab (Soliris®) Supplemental Dose with Concomitant IVIg

IVIg Frequency	Most Recent Soliris® Dose	Supplemental Soliris® Dose per IVIg Cycle	Timing of Supplemental Soliris® Dose
Acute rescue therapy	No supplemental SOLIRIS dose needed		
Equal to or more frequent than every 4 weeks	900 mg or more	600 mg	At the same time as scheduled SOLIRIS® dose
	600 mg or less	300 mg	
Less frequent than every 4 weeks	900 mg or more	600 mg	At the next scheduled SOLIRIS® dose after the last IVIg cycle
	600 mg or less	300 mg	

Eculizumab-aagh (EPYSQLI®)

Administration: Eculizumab-aagh (EPYSQLI®) is available as a 300 mg/30 mL (10 mg/mL) single-dose vial and intended to be administered as an intravenous infusion only.

- Vaccinate patients against meningococcal infection (serogroups A, C, W, Y, and B) according to current ACIP recommendations at least 2 weeks prior to initiation of EPYSQLI®.
- Administer over 35 minutes in adults and 1-4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Do not administer an intravenous pump or bolus injection.
- Dilute EPYSQLI® to a final admixture concentration of 5 mg/mL with 0.9% Sodium Chloride, 0.45% Sodium Chloride, or 5% Dextrose in Water.
- Administer EPYSQLI® at the recommended dosage regimen time points, or within two days of these time points.

EPYSQLI® Recommended Dosage Regimen – PNH (For patients 18 years of age and older)

- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter

EPYSQLI® Recommended Dosage Regimen – aHUS (For patients 18 years of age and older)

- 900 mg weekly for the first 4 weeks, followed by
- 1,200 mg for the fifth dose 1 week later, then
- 1,200 mg every 2 weeks thereafter

EPYSQLI® Dosing Recommendation in aHUS Patients Less than 18 Years of Age:

- Administer EPYSQLI® based on body weight

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1,200 mg at week 5; then 1,200 mg every 2 weeks
30 kg – less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg – less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg – less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg – less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

EPYSQLI® Recommended Dosage Regimen – gMG (For patients 18 years of age and older)

- 900 mg weekly for the first 4 weeks, followed by
- 1,200 mg for the fifth dose 1 week later, then
- 1,200 mg every 2 weeks thereafter

EPYSQLI® Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

Type of Plasma Intervention	Most Recent EPYSQLI® Dose	Supplemental EPYSQLI® Dose with Each Plasma Intervention	Timing of Supplemental EPYSQLI® Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥ 600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥ 300 mg	300 mg per infusion of fresh	60 minutes prior to each infusion of fresh frozen plasma

Eculizumab-aeeb (BKEMV®)

Administration: BKEMV® is available as a 300 mg/30 mL (10 mg/mL) single-dose vial and is intended to be administered as an intravenous infusion only.

- Vaccinate patients against meningococcal infection (serogroups A, C, W, Y and B) according to current ACIP recommendations at least 2 weeks prior to initiation of BKEMV®.
- Administer the BKEMV® admixture by intravenous infusion over 35 minutes in adults and 1-4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Do not administer as an intravenous push or bolus injection.
- Dilute BKEMV® to a final concentration of 5 mg/mL by adding the appropriate amount of 0.9% Sodium Chloride, 0.45% Sodium Chloride, 5% Dextrose in Water, or Ringer's Injection to the inf infusion bag.
- Administer BKEMV® at the recommended dosage regimen time points, or within two days of these time points.

BKEMV® Recommended Dosage Regimen – PNH (For patients 18 years of age or older)

- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter

BKEMV® Recommended Dosage Regimen – aHUS (For patients 18 years of age or older)

- 900 mg weekly for the first 4 weeks, followed by
- 1,200 mg for the fifth dose 1 week later, then
- 1,200 mg every 2 weeks thereafter

BKEMV® Dosing Recommendations in aHUS Patients Less than 18 Years of Age

- Administer BKEMV® based on patient's body weight

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly × 4 doses	1,200 mg at week 5; then 1,200 mg every 2 weeks
30 kg – less than 40 kg	600 mg weekly × 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg – less than 30 kg	600 mg weekly × 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg – less than 20 kg	600 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg – less than 10 kg	300 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 3 weeks

BKEMV® Recommended Dosage Regimen – gMG (For patients 18 years of age or older)

- 900 mg weekly for the first 4 weeks, followed by
- 1,200 mg for the fifth dose 1 week later, then
- 1,200 mg every 2 weeks thereafter

BKEMV® Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

Type of Plasma Intervention	Most Recent BKEMV® Dose	Supplemental BKEMV® Fose with Each Plasma Intervention	Timing of Supplemental BKEMV® Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or	Within 60 minutes after each

	600 mg or greater	plasma exchange session 600 mg per each plasmapheresis or plasma exchange session	plasmapheresis or plasma exchange
Fresh frozen plasma infusion	300 mg or greater	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Ravulizumab (Ultomiris®)Administration: Ravulizumab (Ultomiris®) is intended to be administered only as an intravenous infusion through a 0.2- or 0.22-micron filter in adult or pediatric patients one month of age and older. Ravulizumab (Ultomiris®) is available as 300 mg/3 mL (100 mg/mL) or 1,100 mg/11 mL (100 mg/mL) solution in a single-dose vial.

- Vaccinate patients against meningococcal infection (serogroups A, C, W, Y and B) according to current ACIP recommendations at least 2 weeks prior to initiation of Ravulizumab (Ultomiris®).
- The product must be protected from light. Ravulizumab (Ultomiris®) must be diluted to a final concentration of 50 mg/mL.
- After administration, flush the entire line with 0.9% Sodium Chloride.

Ravulizumab (Ultomiris) IV Administration Weight-Based Dosing Regimen for PNH, aHUS, gMB, or NMOSD

INDICATIONS	BODY WEIGHT RANGE (kg)	LOADING DOSE (mg)	MAINTENANCE DOSE (mg)	DOSING INTERVAL
PNH or aHUS	5 to less than 10	600	300	Every 4 weeks
	10 to less than 20	600	600	
	20 to less than 30	900	2,100	Every 8 weeks
	30 to less than 40	1,200	2,700	
	40 to less than 60	2,400	3,000	

PNH, aHUS, gMG, or NMOSD	60 to less than 100	2,700	3,300	
	100 or greater	3,000	3,600	

Ravulizumab-cwvz (Ultomiris) IV Administration Treatment Initiation Instructions- PNH, aHUS, gMG, or NMOSD

Population	Weight-based loading dose	Time of First Weight-based Maintenance Dose
Not currently on Ultomiris® or eculizumab treatment.	At treatment start	2 weeks after Ultomiris® loading dose
Currently treated with eculizumab	At time of next scheduled eculizumab dose	2 weeks after Ultomiris® loading dose

Ravulizumab-cwvz (Ultomiris) Supplemental Dose after PE, PP, or IVIg

BODY WEIGHT RANGE (kg)	MOST RECENT UULTOMIRIS DOSE (mg)	SUPPLEMENTAL DOSE (mg) FOLLOWING EACH PE OR PP INTERVENTION	SUPPLEMENTAL DOSE (mg) FOLLOWING COMPLETETION OF AN IVIg CYCLE
40 to less than 60	2,400	1,200	600
	3,000	1,500	
60 to less than 100	2,700	1,500	600
	3,300	1,800	
100 or greater	3,000	1,500	600
	3,600	1,800	
Timing of Supplemental Dose		Within 4 hours following each PE or PP intervention	Within 4 hours following completion of IVIg cycle

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.

BACKGROUND

Eculizumab (Soliris®), Eculizumab-aeeb (BKEMV®), Eculizumab-aagh (EPYSQLI®), 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. Both complement inhibitors are approved for the treatment of Generalized Myasthenia Gravis and Neuromyelitis Optica Spectrum Disorder (NMOSD).

Eculizumab (Soliris®), Eculizumab-aeeb (BKEMV®), Eculizumab-aagh (EPYSQLI®), 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]

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.

Eculizumab (Soliris®)

On March 19, 2007, Alexion Pharmaceuticals, Inc., announced that it has received marketing approval from the U.S. Food and Drug Administration (FDA) for Soliris (eculizumab). Soliris is the first therapy approved for paroxysmal nocturnal hemoglobinuria (PNH), a rare, disabling and life-threatening blood disorder defined by chronic red blood cell destruction, or hemolysis. Soliris is indicated for the treatment of patients with PNH to reduce hemolysis.

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 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.

Eculizumab-aeeb (BKEMV®)

On May 28, 2024, the U.S. Food and Drug Administration (FDA) approved Eculizumab-aeeb (BKEMV®) as the first interchangeable biosimilar to Soliris® (Eculizumab) to treat certain rare diseases. Eculizumab-aeeb (BKEMV®) is approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

Eculizumab-aagh (EPYSQLI®)

On July 19, 2024, the U.S. Food and Drug Administration (FDA) approved Eculizumab-aagh (EPYSQLI®) as a biosimilar to Soliris® (Eculizumab). Eculizumab-aagh (EPYSQLI®) has been approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Eculizumab-aagh (EPYSQLI®) is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Ravulizumab (Ultomiris®)

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).

On October 18, 2019, Alexion Pharmaceuticals, Inc announced that the U.S. Food and Drug Administration (FDA) approved Ultomiris (ravulizumab-cwvz) for the treatment of atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) for adult and pediatric (one month of age and older) patients.

On October 12, 2020, Alexion Pharmaceuticals, Inc announced that the U.S. Food and Drug Administration (FDA) has approved Ultomiris (ravulizumab-cwvz) 100 mg/mL formulation for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH) and for atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy for adult and pediatric (one month of age and older) patients.

On June 7, 2021 Alexion Pharmaceuticals, Inc announced that the U.S. Food and Drug Administration (FDA) has approved the expanded use of Ultomiris (ravulizumab-cwvz) to include children (one month of age and older) and adolescents with paroxysmal nocturnal hemoglobinuria (PNH).

On April 28, 2022, Ultomiris (ravulizumab-cwvz) has been approved in the US for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive

On March 25, 2024 Ultomiris (ravulizumab-cwvz) has been approved in the United States (US) as the first and only long-acting C5 complement inhibitor for the treatment of adult patients with anti-aquaporin-4 (AQP4) antibody-positive (Ab+) neuromyelitis optica spectrum disorder (NMOSD).

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®), Eculizumab-aeeb (BKEMV®), and Eculizumab-aagh (EPYSQLI®) 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, most 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 day 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. 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). 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 (gMG)

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).

The efficacy of ULTOMIRIS for the treatment of gMG was demonstrated in a randomized, double-blind, placebo-controlled, multicenter study. Patients were randomized 1:1 to either receive ULTOMIRIS (n=86) or placebo (n=89) for 26 weeks. ULTOMIRIS was administered intravenously according to the weight-based recommended dosage.

The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score at Week 26. The MG-ADL assess the impact on daily function of 8 signs or symptoms that are common in gMG. Each item was scored 0 out of 3, where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. The total score ranges from 0 to 24, with the higher scores indicating more impairment. The secondary endpoints, also assessed from baseline to Week 26, included the change in the Quantitative MG total score (QMG). The QMG is a 13-item categorical scale assessing muscle weakness. Each item was also scored 0-3, where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total score ranges from 0 to 39, where higher scores indicate more severe impairment. Other secondary endpoints included the

proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively.

Treatment with ULTOMIRIS demonstrated a statistically significant change in the MG-ADL and QMG total scores from baseline at Week 26 as compared to placebo. The proportion of QMG responders and MG-ADL at week 26 was greater for ULTOMIRIS [(30.0%) compared to placebo (11.3%) p = 0.005 and (56.7%) compared to placebo (34.1%) respectively].

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

A randomized placebo-controlled trial (NMSOD Study 1) was conducted for the efficacy of SOLIRIS for the treatment of NMOSD. Enrolled. There were 143 patients enrolled with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening: History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening, Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid), on immunosuppressive therapy (IST), on a stable dose regimen, the use of concurrent corticosteroids was limited to 20 mg per day or less, Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIg within 3 weeks prior to screening. A total of 96 patients were randomized to receive SOLIRIS treatment and 47 were randomized to receive placebo. The primary endpoint for NMOSD Study 1 was the time to the first adjudicated on-trial relapse. The time to the first adjudicated on-trial relapse was significantly longer those that received SOLIRIS-compared to placebo-treated patients (relative risk reduction 94%; hazard ratio 0.058; p < 0.0001) SOLIRIS-treated patients experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant treatment. SOLIRIS-treated patients had a 96% relative reduction in the adjudicated on-trial annualized relapse rate (ARR) compared to patients on placebo. Compared to placebo-treated patients, SOLIRIS-treated patients had reduced annualized rates of hospitalizations (0.04 for SOLIRIS versus 0.31 for placebo), of corticosteroid administrations to treat acute relapses (0.07 for SOLIRIS versus 0.42 for placebo), and of plasma exchange treatments (0.02 for SOLIRIS versus 0.19 for placebo).

An open label multicenter study was conducted to assess the efficacy and safety of ULTOMIRIS in adult patients with anti-AQP4 antibody positive NMOSD. Patients participating in the study received ULTOMIRIS intravenously in the Primary Treatment Period that ended when the last enrolled patient completed (or discontinued prior to) 50 weeks on study, representing a median study duration of 73.5 weeks. Efficacy assessments were based on a comparison of patients in the study with an external placebo control group from another study (Study ECU-NMO301, NCT01892345) composed of a comparable population of adult patients with antiAQP4 antibody positive NMOSD. There were 58 adult patients enrolled with NMOSD who had a positive serologic test for anti-AQP4 antibodies, at least 1 relapse in the last 12 months prior to the Screening Period, and an Expanded Disability Status Scale (EDSS) score ≤ 7. In the external placebo control group, eligibility criteria were similar except patients were required to have at least 2 relapses in last 12 months or 3 relapses in the last 24 months 43 with at least 1 relapse in

the 12 months prior to screening. Previous treatment on immunosuppressant therapies (ISTs) was not required for enrollment. However, patients on selected ISTs (i.e., corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus) were permitted to continue therapy, with a requirement for stable dosing until they reached Week 106 in the Study. Similar IST use was permitted in the external placebo control group.

The primary endpoint of Study ALXN1210-NMO-307 was the time to first adjudicated on-trial relapse as determined by an independent adjudication committee. No adjudicated 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 adjudicated on-trial relapse ($p < 0.0001$). 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 adjudicated on-trial relapse with or without concomitant treatment.

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 Code	Description
N/A	N/A

HCPCS Code	Description
J1299	Injection, Eculizumab, 2 mg
J1303	Injection, Ravulizumab, 10mg

Q5151	Injection, eculizumab-aagh (Epysqli), biosimilar, 2 mg
Q5152	Injection, eculizumab-aeeb (Bkemv), biosimilar, 2 mg

ICD-10 Codes	Description
D59.30-D59.39	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 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 Health Partners Plans Medicaid and Health Partners Plans 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
2025 Ad-hoc review, Drug names added, Revisions to FDA indications, Prior authorization criteria, Dosage & Administration, Black box warning, Coding and Background sections. References updated.	G	12/17/2025
2025 review. ICD-10 and HCPCS codes added. References updated.	F	04/17/2025
2024 Annual review. New indication added for Ultomiris. Dosing regimens updated for Soliris and Ultomiris by indication. Removed Subcutaneous formulation dosing from Ultomiris. Revised Criteria for Soliris and Ultomiris is accordance with updated Prescribing Information. Added Clinical Studies for Soliris and Ultomiris. Minor formatting changes. Reference updated.	E	11/20/2024
2023 Annual review. Minor formatting changes. Dosing regimen for Soliris updated. References updated.	D	12/1/2023
Policy updated due to new FDA labeling.	C	12/1/2022
Annual review. Policy statement revised for clarity.	B	04/01/2022
Annual review. No changes for 2021.	A	07/01/2020
New policy.	A	07/01/2020

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