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Policy Number: 040.005
Title: Coverage Determination Policy for Complement Inhibitors: Soliris (Eculizumab); Ultomiris (Ravulizumab)

Regions: ☒ Texas ☒ New Mexico

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

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WELLMED
Doctors helping patients for more than 25 years

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Coverage Policy Number: 040.005

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

Paroxysmal Nocturnal Hemoglobinuria (PNH): **Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz)** are medically necessary for the treatment of paroxysmal Nocturnal Hemoglobinuria (PNH) when **ALL** of the following criteria are met:

A. Documentation supporting the diagnosis of Paroxysmal Nocturnal Hemoglobinuria that includes BOTH of the following:

I. Flow cytometry analysis confirming presence of PNH clones

II. Laboratory results, signs, and/or symptoms attributed to PNH (e.g., abdominal pain, anemia, dyspnea, extreme fatigue, smooth muscle dystonia, unexplained/unusual thrombosis, hemolysis/hemoglobinuria, kidney disease, pulmonary hypertension, etc.)

B. Patient is treatment naïve with BOTH Soliris and Ultomiris

C. Patient is NOT receiving Soliris or Ultomiris in combination with Empaveli (pegcetacoplan)

D. Soliris or Ultomiris are dosed according to the US FDA labeled dosing for PNH

E. Prescribed by, or in consultation with a hematologist or oncologist

F. Initial authorization will be for no more than 6 months

Atypical Hemolytic uremic syndrome (aHUS): Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) are medically necessary for the treatment of atypical Hemolytic Uremic Syndrome (aHUS) when **ALL** of the following criteria are met:

A. Documentation supporting the diagnosis of aHUS by ruling out BOTH of the following:

I. Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS)

II. Thrombotic thrombocytopenia purpura (TTP) (e.g., rule out ADAMTS13 deficiency)

B. Laboratory results, signs, and/or symptoms attributed to aHUS (e.g., thrombocytopenia, microangiopathic hemolysis, thrombotic microangiopathy, acute renal failure, etc.)

C. Patient is treatment naïve with BOTH Soliris and Ultomiris

D. Soliris or Ultomiris is dosed according to the US FDA labeled dosing for aHUS

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

F. Initial authorization will be for no more than 6 months

Myasthenia gravis, generalized (gMG): **Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz)** are medically necessary for the treatment of generalized Myasthenia Gravis when **ALL** of the following criteria are met:

A. Submission of medical records (e.g., chart notes, laboratory values, etc.) to support the diagnosis of generalized myasthenia gravis (gMG) by a neurologist or in consultation with a neurologist confirming all of the following:

I. Patient has not failed a previous course of Soliris therapy

II. Patient has not failed a previous course of Ultomiris therapy

III. Positive serologic test for anti-AChR antibodies

IV. ONE of the following:

a. History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation

b. History of positive anticholinesterase test (e.g., edrophonium chloride test)

c. Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating neurologist

V. Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II, III, or IV at initiation of therapy

VI. Patient has a Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL) total score ≥ 6 at initiation of therapy

B. ONE of the following:

I. History of failure of at least two immunosuppressive agents over the course of at least 12 months [e.g., azathioprine, corticosteroids, methotrexate, cyclosporine, mycophenolate, etc.] or

II. Patient has a history of failure of at least one immunosuppressive therapy and has required four or more courses of plasmapheresis/ plasma exchanges and/or intravenous immune globulin over the course of at least 12 months without symptom control

C. Soliris or Ultomiris is initiated and titrated according to the US FDA labeled dosing for gMG

D. Patient is NOT receiving Soliris or Ultomiris in combination with a neonatal Fc receptor blocker [e.g., Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Rystiggo (rozanolixizumab-noli)]

E. Prescribed by, or in consultation with, a neurologist

F. Initial authorization will be for no more than 6 months

Neuromyelitis optica spectrum disorder (NMOSD), when **ALL** of the following criteria are met: ***Soliris (eculizumab) Only***

A. Submission of medical records (e.g., chart notes, laboratory values, etc.) to support the diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming **ALL** of the following

I. Past medical history of ONE of the following

a. Optic neuritis

b. Acute myelitis

c. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting

d. Acute brainstem syndrome

e. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions

f. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

II. Positive serologic test for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies

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

B. Patient has NOT failed a previous course of Soliris therapy

C. History of failure, of contraindication, or intolerance to rituximab therapy

D. ONE of the following:

I. History of at least two relapses during the previous 12 months prior to initiating Soliris

II. History of at least three relapses during the previous 24 months, at least one relapse occurring within the past 12 months prior to initiating Soliris

E. Soliris is initiated and titrated according to the US FDA labeled dosing for NMOSD

F. Patient is NOT receiving Soliris in combination with ANY of the following:

I. Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]

II. Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab)]

III. B-cell depletion therapy [e.g., rituximab, Uplizna (inebilizumb-cdon)]

G. Prescribed by, or in consultation with, a neurologist

H. Initial authorization will be for no more than 6 months

NOTE:

Soliris and Ultomiris are **unproven and not medically necessary** for **ANY** the following conditions:

A. Treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS) or the

B. Treatment of adult patients with generalized Myasthenia Gravis (gMG) who are NOT anti-acetylcholine receptor (AchR) antibody positive

Renewal/Continuation of Therapy Requests

RENEWAL requests for continued use of **Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz)** will be approved when the following criteria are met:

For Paroxysmal Nocturnal Hemoglobinuria (PNH), ALL of the following must be met:

- **A.** Patient has previously been treated with Soliris or Ultomiris
- **B.** Documentation demonstrating a positive clinical response from baseline (e.g., increased or stabilization of hemoglobin levels, reduction in transfusions, improvement in hemolysis, decrease in LDH, increased reticulocyte count, etc.)
- **C.** ONE of the following
  - I. Patient is < 18 years of age
  - II. Patient is pregnant
  - III. BOTH of the following:
    - a. Patient has a hemoglobin level greater than 10.5 g/dL
    - b. Patient has not required red blood cell transfusions to maintain a hemoglobin level greater than 10.5 g/dL
  - IV. BOTH of the following:
    - a. Prescriber attests that the patient has been counseled on alternative chronic treatment options for PNH
    - b. Prescriber attests that the patient has shared in decision-making on their PNH therapy plan
- **D.** Soliris or Ultomiris is dosed according to the US FDA labeled dosing for PNH
- **E.** Patient is NOT receiving Soliris or Ultomiris in combination with Empaveli (pegcetacoplan)
- **F.** Prescribed by, or in consultation with, a hematologist or oncologist;
- **G.** Reauthorization will be for no more than 12 months

For Atypical Hemolytic Uremic Syndrome (aHUS), ALL of the following must be met:

- **A.** Patient has previously been treated with Soliris or Ultomiris
- **B.** Documentation demonstrating a positive clinical response from baseline (e.g., reduction of plasma exchanges, reduction of dialysis, increased platelet count, reduction of hemolysis)
- **C.** Soliris or Ultomiris is dosed according to the US FDA labeled dosing for aHUS
- **D.** Prescribed by, or in consultation with, a hematologist or nephrologist
- **E.** Reauthorization will be for no more than 12 months

For Generalized Myasthenia Gravis (gMG), ALL of the following must be met:

- **A.** Patient has previously been treated with Soliris or Ultomiris
- **B.** Submission of medical records (e.g., chart notes, laboratory tests) to demonstrate a positive clinical response from baseline as demonstrated by at least all of the following
  - I. Improvement and/or maintenance of at least a 2-point improvement (reduction in score) in the MG-ADL score from pre-treatment baseline
  - II. Reduction in signs and symptoms of myasthenia gravis
  - III. Maintenance, reduction, or discontinuation of dose(s) of baseline immunosuppressive therapy (IST) prior to starting Soliris or Ultomiris. *Note: Add on, dose escalation of IST, or additional rescue therapy from baseline to treat myasthenia gravis or exacerbation of symptoms while on Soliris or Ultomiris therapy will be considered as treatment failure*
- **C.** Soliris or Ultomiris is dosed according to the US FDA labeled dosing for gMG
- **D.** Patient is NOT receiving Soliris or Ultomiris in combination with a neonatal Fc receptor blocker [e.g., Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Rystiggo (rozanolixizumab-noli)]
- **E.** Prescribed by, or in consultation with, a neurologist
- **F.** Reauthorization will be for no more than 12 months

For Neuromyelitis Optica Spectrum Disorder (NMOSD), ALL of the following must be met:

Soliris (eculizumab) Only

A. Patient has previously been treated with Soliris

B. Submission of medical records (e.g., chart notes, laboratory tests) to demonstrate a positive clinical response from baseline as demonstrated by at least both of the following:

I. Reduction in the number and/or severity of relapses or signs and symptoms of NMOSD

II. Maintenance, reduction, or discontinuation of dose(s) of any baseline immunosuppressive therapy (IST) prior to starting Soliris. *Note: Add on, dose escalation of IST, or additional rescue therapy from baseline to treat NMOSD or exacerbation of symptoms while on Soliris therapy will be considered as treatment failure*

C. Soliris is dosed according to the US FDA labeled dosing for NMOSD

D. Patient is NOT receiving Soliris in combination with ANY of the following

I. Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]

II. Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab]

III. B-cell depletion therapy [e.g., rituximab, Uplizna (inebilizumb-cdon)]

E. Prescribed by, or in consultation with, a neurologist

F. Reauthorization will be for no more than 12 months

FDA Approved Dose and Indication

Product	Indication	Dosing
Ultomiris **See tables below for Supplemental dosing*	Atypical Hemolytic Uremic Syndrome (aHUS)	• (20 to less than 30 kg) Loading, 900 mg IV infusion; maintenance, 2100 mg 2 weeks after loading dose then every 8 weeks • (30 to less than 40 kg) Loading, 1200 mg IV infusion; maintenance, 2700 mg 2 weeks after loading dose then every 8 weeks • (40 to less than 60 kg) Loading, 2400 mg IV infusion; maintenance, 3000 mg 2 weeks after loading dose then every 8 weeks • (60 to less than 100 kg) Loading, 2700 mg IV infusion; maintenance, 3300 mg 2 weeks after loading dose then every 8 weeks • (100 kg or greater) Loading, 3000 mg IV infusion; maintenance, 3600 mg 2 weeks after loading dose then every 8 weeks • (SubQ, 40 kg or greater) Maintenance, 490 mg subQ once weekly starting 2 weeks after IV loading dose; deliver via 2 on-body subQ delivery systems (245 mg from each system) • Duration of therapy: At least 6 months; individualize treatment beyond 6 months • Switching from eculizumab; administer loading dose at the time of the next scheduled eculizumab dose, then administer maintenance doses (IV or subQ) starting 2 weeks after the loading dose • Switching from IV to subQ, initiate the subQ maintenance dosage 8 weeks after the last the IV maintenance dose • Switching from subQ to IV, initiate the IV maintenance dosage 1 week after last the subQ maintenance dose

Ultomiris **See tables below for Supplemental dosing*	Paroxysmal Nocturnal Hemoglobinuria (PNH)	• (20 to less than 30 kg) Loading, 900 mg IV infusion; maintenance, 2100 mg 2 weeks after loading dose then every 8 weeks • (30 to less than 40 kg) Loading, 1200 mg IV infusion; maintenance, 2700 mg 2 weeks after loading dose then every 8 weeks • (40 to less than 60 kg) Loading, 2400 mg IV infusion; maintenance, 3000 mg 2 weeks after loading dose then every 8 weeks • (60 to less than 100 kg) Loading, 2700 mg IV infusion; maintenance, 3300 mg 2 weeks after loading dose then every 8 weeks • (100 kg or greater) Loading, 3000 mg IV infusion; maintenance, 3600 mg 2 weeks after loading dose then every 8 weeks beginning 2 weeks after loading dose • (SubQ, 40 kg or greater) 490 mg subQ once weekly starting 2 weeks after IV loading dose; deliver via 2 on-body subQ delivery systems (245 mg from each system • Duration of therapy: At least 6 months; individualize treatment beyond 6 months • Switching from eculizumab, administer loading dose at the time of the next scheduled eculizumab dose, then administer maintenance doses (IV or subQ) starting 2 weeks after the loading dose • Switching from IV to subQ, initiate the subQ maintenance dosage 8 weeks after the last the IV maintenance dose • Switching from subQ to IV, initiate the IV maintenance dosage 1 week after last the subQ maintenance dose
Ultomiris **See tables below for Supplemental dosing*	Myasthenia gravis, Anti-acetylcholine receptor antibody positive (gMG)	• (40 to less than 60 kg) Loading, 2400 mg IV infusion; maintenance, 3000 mg IV starting 2 weeks after loading dose, then every 8 weeks • (60 to less than 100 kg) Loading, 2700 mg IV infusion; maintenance, 3300 mg IV starting 2 weeks after loading dose, then every 8 weeks

		• (100 kg or greater) Loading, 3000 mg IV infusion; maintenance, 3600 mg IV starting 2 weeks after loading dose, then every 8 weeks • Switching from eculizumab, administer IV loading dose at the time of the next scheduled eculizumab dose, then initiate the IV maintenance dosage 2 weeks after the IV loading dose
Soliris **See tables below for Supplemental dosing*	Atypical Hemolytic Uremic Syndrome (aHUS)	• Initial, 900 mg by IV infusion weekly for 4 weeks; maintenance, 1200 mg for the fifth dose 1 week later, and then 1200 mg every 2 weeks thereafter
	Paroxysmal Nocturnal Hemoglobinuria (PNH)	• Initial, 600 mg by IV infusion weekly for 4 weeks; maintenance, 900 mg for the fifth dose 1 week later, and then 900 mg every 2 weeks thereafter
	Myasthenia gravis, Anti-acetylcholine receptor antibody positive (gMG)	• 900 mg IV once a week for 4 weeks, 1200 mg IV on week 5, then 1200 mg IV every 2 weeks thereafter; give within 2 days of regimen time points
	Neuromyelitis optica spectrum disorder, Anti-aquaporin-4 (AQP4) antibody positive	• 900 mg IV once a week for 4 weeks, 1200 mg IV on week 5, then 1200 mg IV every 2 weeks thereafter; give within 2 days of regimen time points

Supplemental Dosing

1) For patients with aHUS, gMG, or NMOSD, supplementation dosing of **Soliris** may be required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion (PE/PI). Please refer to table below[1].

Table 2: Supplemental Dose of Soliris after PE/PI

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

2) For patients receiving **Ultomiris**: Plasma exchange (PE), plasmapheresis (PP), and intravenous immunoglobulin (IVIG) have been shown to reduce ULTOMIRIS serum levels. A supplemental dose of ULTOMIRIS is required in the setting of PE, PP, or IVIG. Refer to table below[19].

Table 4: Supplemental Dose of ULTOMIRIS after PE, PP, or IVIg*

Body Weight Range (kg)	Most Recent ULTOMIRIS Dose (mg)	Supplemental Dose (mg) following each PE or PP Intervention	Supplemental Dose (mg) following Completion 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 ULTOMIRIS Supplemental Dose		Within 4 hours following each PE or PP intervention	Within 4 hours following completion of an IVIg cycle

General Background

Soliris is a complement inhibitor indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis, treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy, and treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive. Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Vaccinate for meningococcal disease according to the most current Advisory Committee onImmunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations, considering the duration of Soliris therapy. Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris. If urgent Soliris therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible.

Soliris is contraindicated in patients with unresolved serious Neisseria meningitidis infection and patient patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection.

Discontinuation of Soliris can lead to disease manifestation. For patients with PNH monitor for at least 8 weeks following discontinuation for hemolysis. In patients with aHUS monitor for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical trials, 18 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was reinitiated in 4 of these 5 patients. If TMA complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion], or appropriate organ-specific supportive measures. Soliris is available only through a restricted distribution program (REMS).

Ravulizumab-cwvz is a humanized monoclonal antibody terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b9. Ravulizumab-cwvz inhibits terminal complement-mediated intravascular hemolysis in patients with Paroxysmal nocturnal hemoglobinuria (PNH) and complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic uremic syndrome (aHUS).

Ravulizumab-cwvz is indicated to treat adults and pediatric patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA). In patients naïve to complement inhibitor treatment, a complete TMA response was achieved in 54% of adults and 71% of pediatric patients after 26 weeks of ravulizumab-cwvz treatment in single-arm trials.

Ravulizumab-cwvz is also indicated in adults for the treatment of paroxysmal nocturnal hemoglobinuria. Efficacy and noninferiority to eculizumab was established in patients who were complement inhibitor naïve and in patients who were clinically stable with at least 6 months of eculizumab therapy prior to switching to ravulizumab-cwvz.

Black Box Warning: Serious Meningococcal Infections

Life-threatening meningococcal infections/sepsis have occurred in patients treated with eculizumab and ravulizumab-cwvz. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies. Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of eculizumab and ravulizumab-cwvz, unless the risks of delaying eculizumab and ravulizumab-cwvz therapy outweigh the risk of developing a meningococcal infection. Vaccination reduces, but does not eliminate, the risk of meningococcal infections Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected. Eculizumab and Ravulizumab-cwvz are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the eculizumab and ravulizumab-cwvz REMS, prescribers must enroll in the program.

Clinical Evidence

For Paroxysmal Nocturnal Hemoglobinuria (PNH):
The terminal complement inhibitor eculizumab was recently shown to be effective and well tolerated in patients with paroxysmal nocturnal hemoglobinuria (PNH). Here, we extended these observations with results from an open-label, non-placebo-controlled, 52-week, phase 3 clinical safety and efficacy study evaluating eculizumab in a broader PNH patient population. Eculizumab was administered by intravenous infusion at 600 mg every 7 ± 2 days for 4 weeks; 900 mg 7 ± 2 days later; followed by 900 mg every 14 ± 2 days for a total treatment period of 52 weeks. Ninety-seven patients at 33 international sites were enrolled. Patients treated with eculizumab responded with an 87% reduction in hemolysis, as measured by lactate dehydrogenase levels ($P < .001$). Baseline fatigue scores in the FACIT-Fatigue instrument improved by 12.2 ± 1.1 points ($P < .001$). Eculizumab treatment led to an improvement in anemia. The increase in hemoglobin level occurred despite a reduction in transfusion requirements from a median of 8.0 units of packed red cells per patient before treatment to 0.0 units per patient during the study ($P < .001$). Overall, transfusions were reduced 52% from a mean of 12.3 to 5.9 units of packed red cells per patient. Forty-nine patients (51%) achieved transfusion independence for the entire 52-week period. Improvements in hemolysis, fatigue, and transfusion requirements with eculizumab were independent of baseline levels of hemolysis and degree of thrombocytopenia. Quality of life measures were also broadly improved with eculizumab treatment. This study demonstrates that the beneficial effects of eculizumab treatment in patients with PNH are applicable to a broader population of PNH patients than previously studied. Inform patients with PNH that they may develop hemolysis due to PNH when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following Soliris discontinuation.[3]

For Atypical Hemolytic Uremic Syndrome (aHUS):
Although plasma exchange or infusion has been used to manage atypical hemolytic–uremic syndrome and may transiently maintain a normal platelet count and lactate dehydrogenase level in some patients, the underlying complement dysregulation and thrombotic microangiopathic processes are likely to persist. Indeed, end-stage renal disease (ESRD) or death occurs in approximately 33 to 40% of patients during the first clinical manifestation of atypical hemolytic–uremic syndrome. Within 1 year after a diagnosis of this syndrome, up to 65% of patients treated with plasma exchange or infusion sustain permanent renal damage, have progression to ESRD, or die.

Thirty-seven patients with atypical hemolytic–uremic syndrome were enrolled in the trials. For the 17 patients (16 adults and 1 adolescent) with progressive thrombotic microangiopathy who were enrolled in trial 1, the median interval between diagnosis of atypical hemolytic–uremic syndrome and screening was 9.7 months. All patients had substantial renal damage (100% had an estimated GFR of <60 ml per minute per 1.73 m2 of body-surface area for a median of 17 days). All but 1 patient (who could not undergo plasma exchange or infusion because of side effects) received plasma exchange or infusion within 1 week before initiation of treatment with eculizumab. For the 20 patients (15 adults and 5 adolescents) enrolled in trial 2, the interval between diagnosis and screening was longer (median, 48.3 months), and most of the patients had chronic renal insufficiency (90% had an estimated GFR of <60 ml per minute per 1.73 m2

for a median of 299 days) and were receiving long-term plasma exchange or infusion (median duration of treatment, 10.1 months).

In trial 1, patients were treated with eculizumab for 26 weeks. Thirteen patients (76%) continued to receive eculizumab during the extension period. At the data-cutoff point, the median duration of eculizumab treatment was 64 weeks (range, 2 to 90). In trial 2, patients were also treated with eculizumab for 26 weeks, with 19 patients (95%) continuing to receive eculizumab during the extension period. At the data-cutoff point, the median duration of treatment with eculizumab was 62 weeks (range, 26 to 74). A total of 24% of
patients in trial 1 and 35% of patients in trial 2 had no identified complement gene mutation or complement factor H autoantibodies.

In trial 1, eculizumab treatment was associated with a significant absolute increase in the platelet count from baseline to week 26 (mean, 73×109 per liter; 95% confidence interval [CI], 40×109 per liter to 105×109 per liter; P<0.001) and to week 64 (91×109 per liter; 95% CI, 67×109 per liter to 116×109 per liter; P<0.001). The platelet count was significantly increased by day 7 (P=0.03). Fifty-three percent of the patients with an abnormal platelet count at baseline had a normal platelet count (≥150×109 per liter) by day 7, and 87% had platelet counts that remained normal at both weeks 26 and 64. All 13 patients with a low platelet count at baseline who were treated for 26 weeks had normalization of the platelet count by week 26, and in all 13 patients who entered the extension period, platelet counts remained normal through the median treatment duration of 64 weeks.[8]

For Generalized Myasthenia Gravis (gMG):
The efficacy of Soliris for the treatment of gMG was established in gMG Study 1 (NCT01997229), a 26-week randomized, double-blind, parallel-group, placebo-controlled, multicenter trial that enrolled patients who met the following criteria at screening:
1. Positive serologic test for anti-AChR antibodies,
2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV,
3. MG-Activities of Daily Living (MG-ADL) total score ≥6,
4. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIg).
A total of 62 patients were randomized to receive Soliris treatment and 63 were randomized to receive placebo. Baseline characteristics were similar between treatment groups, including age at diagnosis (38 years in each group), gender [66% female (eculizumab) versus 65% female (placebo)], and duration of gMG [9.9 (eculizumab) versus 9.2 (placebo) years]. Over 95% of patients in each group were receiving acetylcholinesterase (AchE) inhibitors, and 98% were receiving immunosuppressant therapies (ISTs).
Approximately 50% of each group had been previously treated with at least 3 ISTs. Soliris was administered according to the recommended dosage regimen [see Dosage and Administration (2.4)]. The primary efficacy endpoint for gMG Study 1 was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss

of ability to perform that function (total score 0-24). A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in MG-ADL total scores [-4.2 points in the Soliris treatedgroup compared with -2.3 points in the placebo-treated group (p=0.006)]. A key secondary endpoint in gMG Study 1 was the change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at Week 26. The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness (total score 0-39). A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in QMG total scores [-4.6 points in the Soliris-treated group compared with -1.6 points in the placebo treated group (p=0.001)].[6]

Generalized Myasthenia Gravis (gMG)[19]

Adult Population with gMG

Treated with Intravenous ULTOMIRIS The safety of ULTOMIRIS has been evaluated in 175 adult patients with gMG, including 169 patients who received at least one dose of intravenously administered ULTOMIRIS, 142 patients who were exposed for at least 6 months, and 95 who were exposed for at least 12 months [see Clinical Studies (14.3)]. In a randomized, double-blind, placebo- controlled trial (ALXN1210-MG-306), the most frequent adverse reactions (≥ 10%) with ULTOMIRIS were diarrhea and upper respiratory tract infection. Table 17 describes adverse reactions that occurred at a rate of 5% or more and at greater frequency than placebo. Serious adverse reactions were reported in 20 (23%) patients with gMG receiving ULTOMIRIS and in 14 (16%) patients receiving placebo. The most frequent serious adverse reactions were infections reported in at least 8 (9%) patients treated with ULTOMIRIS and in 4 (4%) patients treated with placebo [see Warnings and Precautions (5.3)]. Of these infections, one fatal case of COVID-19 pneumonia was identified in a patient treated with ULTOMIRIS and one case of infection led to discontinuation of ULTOMIRIS.

For Neuromyelitis optica spectrum disorder (NMOSD):[1]

Pittock et al conducted a randomized, double-blind, time-to –event trial (PREVENT) evaluating the safety and efficacy of eculizumab for the treatment of aquaporin-4-positive (AQP4-IgG) neuromyelitis optica spectrum disorder (NMOSD). The study enrolled 143 adults, of which 91% of patients were women. Patients wererandomly assigned in a 2:1 ratio to receive either intravenous eculizumab (titrated up to 1,200mg every 2 weeks) or placebo. There was no active control. Patients were allowed to continue background immunosuppressant therapy. Patients were included if they had either a history of at least two relapses during the previous 12 months or three relapses during the previous 24 months, at least one of which had occurred within the previous 12 months, and a score of 7 or less on the EDSS. The primary endpoint was the first adjudicated relapse. Secondary outcomes included the adjudicated annualized relapse rate, quality-oflife measures, and the score on the Expanded Disability Status Scale (EDSS). At baseline, the mean (±SD) annualized relapse rate during the previous 24 months was 1.99±0.94. The primary end point of adjudicated relapse occurred in 3 of 96 patients (3%) in the eculizumab group and in 20 of 47 (43%) in the placebo group (hazard ratio, 0.06; 95% confidence interval [CI], 0.02 to 0.20; P<0.001). The median time until the first adjudicated relapse was not reached in the eculizumab group and was reached at 103 weeks in the placebo group. Most relapses were

of myelitis. The adjudicated annualized relapse rate was 0.02 in the eculizumab group and 0.35 in the placebo group (rate ratio, 0.04; 95% CI, 0.01 to 0.15; P<0.001). The mean change in the EDSS score was –0.18 in the eculizumab group and 0.12 in the placebo group (least-squares mean difference, –0.29; 95% CI, –0.59 to 0.01). Upper respiratory tract infections and headaches were more common in the eculizumab group. There was one death from pulmonary empyema in the eculizumab group.

A complete thrombotic microangiopathy (TMA) response was achieved in 54% of patients after 26 weeks of ravulizumab-cwvz treatment in the single-arm ALXN1210-aHUS-311 trial (N=56) of adults with atypical hemolytic uremic syndrome (aHUS) who displayed signs of TMA and were naïve to complement inhibitor treatment. Complete TMA response was defined as normalization of platelet count and LDH and at least a 25% improvement in serum creatinine, which had to be met a 2 separate assessments at least 28 days apart. Median time to complete TMA response was 86 days (range, 7 to 169 days), and median duration for complete response was 7.97 months (range, 2.52 to 16.69 months). At the 26-week evaluation, 84% of patients had platelet count normalization, 77% had LDH normalization, and 59% had at least a 25% improvement in serum creatinine from baseline. Baseline requirements were a platelet count of 150 X 10(9)/L or less, evidence of hemolysis (eg, elevation in serum LDH), and serum creatinine above ULN or that required dialysis. Baseline findings showed 93% of patients had extra-renal signs or symptoms of aHUS, 71.4% had stage 5 chronic kidney disease, 14% had received a kidney transplant, and 51.8% were on dialysis. Eight patients had evidence of TMA for more than 3 days after childbirth.

Complement Inhibitor Naïve (PNH)

Ravulizumab-cwvz every 8 weeks was noninferior to eculizumab every 2 weeks for avoidance of transfusion (73.6% vs 66.1%) and hemolysis measured by LDH normalization (53.6% vs 49.4%) in a 26-week randomized trial (N=246) of complement inhibitor-naïve adults with paroxysmal nocturnal hemoglobinuria (PNH). There were no significant differences between ravulizumab-cwvz and eculizumab in the mean change in LDH (-76.84 vs -76.02), the mean change in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score (7.07 vs 6.4), the breakthrough hemolysis rate (4% vs 10.7%), or the hemoglobin stabilization rate (68% vs 64.5%). Adverse events were reported in 88% with ravulizumab and 86.8% with eculizumab and included serious events in 8.8% and 7.4%, respectively; the most common adverse events were headache (36% vs 33.1%), nasopharyngitis (8.8% vs 14.9%), nausea (10.4% vs 8.3%), upper respiratory tract infection (10.4% vs 5.8%), and pyrexia (4.8% vs 10.7%). Ravulizumab-cwvz was dosed based on weight with an IV loading dose on day 1, followed by maintenance doses on day 15 and every 8 weeks thereafter. Eculizumab 600-mg induction doses were administered on Days 1, 8, 15, and 22, followed by maintenance dosing with 900 mg on Day 29 and every 2 weeks thereafter (total of 26 week of treatment). All patients had received meningococcal vaccination within 3 years of study drug initiation, and no meningococcal infections occurred.

Eculizumab-experienced (PNH)

Ravulizumab-cwvz every 8 weeks was noninferior to eculizumab every 2 weeks for hemolysis measured by LDH percent change from baseline (-0.82% vs 8.4%) in a 26-week randomized study (N=195) of patients with paroxysmal nocturnal hemoglobinuria (PNH) who were clinically stable and had been treated with eculizumab for at least the past 6 months (mean duration, 5.8 years). Patients either continued eculizumab or switched to ravulizumab-cwvz. There were no significant differences in the breakthrough hemolysis rate (0% vs 5.1%), the mean change from baseline in

Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score (2 vs 0.54), the transfusion avoidance rate (87.6% vs 82.7%), or the hemoglobin stabilization rate (76.3% vs 75.5%). Adverse events were reported in 87.6% with ravulizumab and 87.8% with eculizumab and included serious events in 4.1% and 8.2%, respectively; the most common adverse events were headache (26.8% vs 17.3%), nasopharyngitis (21.6% vs 20.4%), upper respiratory tract infection (18.6% vs 10.2%), and cough (5.2% vs 10.2%). Ravulizumab-cwvz was dosed based on weight with an IV loading dose on day 1, followed by maintenance doses on day 15 and every 8 weeks thereafter. Eculizumab 900-mg maintenance doses were continued every 2 weeks.

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

In 2021, Hillmen et al evaluated the efficacy and safety of pegcetacoplan as compared to eculizumab in adults with PNH and hemoglobin levels below 10.5g/dL despite use of eculizumab for at least 3 months in a phase 3 open label, controlled trial (PEGASUS). All patients received pegcetacoplan plus eculizumab during a 4-week run-in phase, then randomized in a 1:1 ratio to subcutaneous pegcetacoplan monotherapy (n = 41) or intravenous eculizumab (n = 39) for 16 weeks. This period was followed by a 32-week period in which all patients received open-label pegcetacoplan. The primary endpoint was the mean change in hemoglobin level from baseline to week 16. Secondary endpoints include proportion of patients that did not require transfusion during the randomized, controlled period, change from baseline to week 16 in absolute reticulocyte count, lactate dehydrogenase (LDH) legel, and score on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale. Clinical efficacy analysis found that pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level from baseline to week 16 with a mean difference between treatments of 3.84 g/dL (95% confidence interval [CI], 2.33 to 5.34; P < 0.001), with the increase of hemoglobin levels in patients receiving pegcetacoplan monotherapy seen as early as week 2 of the 16-week controlled trial period and maintained throughout the 16-week period. Additionally, 35 patients (85%) in the pegcetacoplan group were transfusion-free, whereas only 6 (15%) in the eculizumab group were transfusion-free (P < 0.001). FACIT–F scores increased with pegcetacoplan by 9.2 points and decreased with eculizumab by 2.7 points (adjusted mean difference of 11.9 points [95% CI, 5.49 to 18.25] at week 16). 73% of patients in the pegcetacoplan group had at least a 3-point increase in FACIT–F scores at week 16, as compared with 0% in the eculizumab group (a 3-point change is considered clinically significant). Noninferiority of pegcetacoplan to eculizumab was shown for the change in absolute reticulocyte count. The researchers concluded that in patients with persistent anemia despite eculizumab therapy, pegcetacoplan was superior to eculizumab with respect to change in baseline hemoglobin levels and improvements in key clinical and hematologic variables, such as decrease in transfusions, and therefore treatment with pegcetacoplan may result in better control of PNH than treatment with eculizumab

HCPCS Code

HCPCS Code	Available Dosage Form	Route of Administration
J1303: Soliris (Eculizumab) 10 mg	Intravenous Solution: 100 MG/1 ML	Intravenous
J1300: Ultomiris (Ravulizumab) 10mg	Intravenous Solution: 10 MG/1 ML	Intravenous

Acronyms

NCD = National Coverage Determination

LCD = Local Coverage Determination

LCA = Local Coverage Article

CMS = Centers for Medicare and Medicaid Services

FDA = Food and Drug Administration

aHUS = Atypical Hemolytic Uremic Syndrome

PNH = Paroxysmal nocturnal hemoglobinuria

TTP = Thrombotic Thrombocytopenia Purpura

TMA = Thrombotic Microangiopathy

REMS = Risk Evaluation and Mitigation Strategy

SAE = Serious adverse events

EDSS=Expanded Disability Status Scale

gMG = Generalized Myasthenia Gravis

ACIP = Advisory Committee on Immunization Practices

AchR = Anti-acetylcholine receptor

IST = Immunosuppressive therapy

PE/PI = Plasma exchange/plasma infusion

IVIG = Intravenous immunoglobulin

LDH = Lactate dehydrogenase

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The following studies and LCDs pertain to the usage of complement inhibitors in the treatment C3 glomerulopathies. While this goes beyond of the scope of this specific coverage policy this information may be useful in some cases

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