Complement Inhibitors (Soliris® & Ultomiris®) (for Louisiana Only)

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Instructions for Use

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Application

This Medical Benefit Drug Policy only applies to the state of Louisiana.

Coverage Rationale

This policy refers only to the following complement inhibitor drug products:
- Soliris (eculizumab)
- Ultomiris (ravulizumab-cwvz)

Zilbrysq (zilucoplan) is a self-administered injection obtained under the member's pharmacy benefit.

Soliris and Ultomiris are proven and medically necessary for the treatment of atypical Hemolytic Uremic Syndrome (aHUS) when all of the following criteria are met:[1,12]
- **Initial Therapy**
  - Documentation supporting the diagnosis of aHUS by ruling out both of the following:
    - Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS); **and**
    - Thrombotic thrombocytopenia purpura (TTP) (e.g., rule out ADAMTS13 deficiency)

    and
  - Laboratory results, signs, and/or symptoms attributed to aHUS (e.g., thrombocytopenia, microangiopathic hemolysis, thrombotic microangiopathy, acute renal failure, etc.); **and**
  - Patient is treatment naïve with both Soliris and Ultomiris; **and**
  - Soliris or Ultomiris is dosed according to the US FDA labeled dosing for aHUS; **and**
  - Prescribed by, or in consultation with, a hematologist or nephrologist; **and**
  - Initial authorization will be for no more than 12 months
- **Continuation of Therapy**
  - Patient has previously been treated with Soliris or Ultomiris; **and**
  - Documentation demonstrating a positive clinical response from baseline (e.g., reduction of plasma exchanges, reduction of dialysis, increased platelet count, reduction of hemolysis); **and**
  - Soliris or Ultomiris is dosed according to the US FDA labeled dosing for aHUS; **and**
  - Prescribed by, or in consultation with, a hematologist or nephrologist; **and**
  - Reauthorization will be for no more than 12 months

Soliris and Ultomiris are unproven and not medically necessary for the treatment of Shiga toxin E. coli-related Hemolytic Uremic Syndrome (STEC-HUS).

Soliris and Ultomiris are proven and medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:[1,12]

- **Initial Therapy**
  - Documentation supporting the diagnosis of PNH that includes **both** of the following:
    - Flow cytometry analysis confirming presence of PNH clones; **and**
    - 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.)

    and
  - Patient is treatment naïve with both Soliris and Ultomiris; **and**
  - Soliris or Ultomiris is dosed according to the US FDA labeled dosing for PNH; **and**
  - Patient is **not** receiving Soliris or Ultomiris in combination with another complement inhibitor [e.g., Empaveli (pegcetacoplan), Fabhalta (iptacopan)]; **and**
  - Prescribed by, or in consultation with, a hematologist or oncologist; **and**
  - Initial authorization will be for no more than 12 months
- **Continuation of Therapy**
  - Patient has previously been treated with Soliris or Ultomiris; **and**
  - 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.); **and**
  - Soliris or Ultomiris is dosed according to the US FDA labeled dosing for PNH; **and**
  - Patient is **not** receiving Soliris or Ultomiris in combination with another complement inhibitor [e.g., Empaveli (pegcetacoplan), Fabhalta (iptacopan)]; **and**
  - Prescribed by, or in consultation with, a hematologist or oncologist; **and**
  - Reauthorization will be for no more than 12 months

Soliris and Ultomiris are proven and medically necessary for the treatment of generalized myasthenia gravis in patients who are anti-AChR antibody positive when all of the following criteria are met:[1,9,11,12,36,37]

- **Initial Therapy**
  - Submission of medical records (e.g., chart notes, laboratory values, etc.) confirming **all** of the following:
    - Patient has not failed a previous course of Soliris therapy; **and**
    - Patient has not failed a previous course of Ultomiris therapy; **and**
    - Diagnosis of generalized myasthenia gravis (gMG); **and**
    - Positive serologic test for anti-AChR antibodies; **and**
    - Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II, III, or IV at initiation of therapy; **and**
    - Patient has a Myasthenia Gravis Activities of Daily Living scale (MG-ADL) total score ≥ 6 at initiation of therapy

    and
  - **One** of the following:
    - History of failure of at least **two** immunosuppressive agents over the course of at least 12 months (e.g., azathioprine, corticosteroids, cyclosporine, methotrexate, mycophenolate); **or**
    - 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

    and
  - Soliris or Ultomiris is initiated and titrated according to the US FDA labeled dosing for gMG; **and**
  - Patient is not receiving Soliris or Ultomiris in combination with another complement inhibitor [e.g., Zilbrysq (Zilucoplan)] or a neonatal Fc receptor blocker [e.g., Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Rystiggo (rozanolixizumab-noli)]; **and**
  - Prescribed by, or in consultation with, a neurologist; **and**
  - Initial authorization will be for no more than 12 months
- **Continuation of Therapy**
  - Patient has previously been treated with Soliris or Ultomiris; **and**
  - Submission of medical records (e.g., chart notes, laboratory tests) demonstrating **all** of the following:
    - Improvement and/or maintenance of at least a 2-point improvement (reduction in score) in the MG-ADL score from pre-treatment baseline[39]; **and**

- Reduction in signs and symptoms of myasthenia gravis; **and**
- 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.

and

- Soliris or Ultomiris is dosed according to the US FDA labeled dosing for gMG; **and**
- Patient is not receiving Soliris or Ultomiris in combination with another complement inhibitor [e.g., Zilbrysq (Zilucoplan)] or a neonatal Fc receptor blocker [e.g., Vyvgart (efgartigimod alfa-fcab), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Rystiggo (rozanolixizumab-noli)]; **and**
- Prescribed by, or in consultation with, a neurologist; **and**
- Reauthorization will be for no more than 12 months

Soliris is proven and medically necessary for the treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:[1,25]

- **Initial Therapy**
  - Diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming **all** of the following:[22-25]
    - Past medical history of **one** of the following:[25]
      - Optic neuritis; **or**
      - Acute myelitis; **or**
      - Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting; **or**
      - Acute brainstem syndrome; **or**
      - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions; **or**
      - Symptomatic cerebral syndrome with NMOSD-typical brain lesions

      and
    - Positive serologic test for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies; **and**
    - Diagnosis of multiple sclerosis or other diagnoses have been ruled out

    and
  - Patient has not failed a previous course of Soliris therapy; **and**
  - History of failure of, contraindication, or intolerance to rituximab therapy;[26-32] **and**
  - **One** of the following:
    - History of at least two relapses during the previous 12 months prior to initiating Soliris; **or**
    - 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

    and
  - Soliris is initiated and titrated according to the US FDA labeled dosing for NMOSD; **and**
  - Prescribed by, or in consultation with, a neurologist; **and**
  - Patient is **not** receiving Soliris in combination with **any** of the following:
    - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]; **or**
    - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab)]; **or**
    - B-cell depletion therapy [e.g., rituximab, Uplizna (inebilizumab-cdon)]

    and
  - Initial authorization will be for no more than 12 months
- **Continuation of Therapy**
  - Patient has previously been treated with Soliris; **and**
  - Documentation of positive clinical response from baseline as demonstrated by at least **both** of the following:
    - Reduction in the number and/or severity of relapses or signs and symptoms of NMOSD; **and**
      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.

    and
  - Soliris is dosed according to the US FDA labeled dosing for NMOSD; **and**
  - Prescribed by, or in consultation with, a neurologist; **and**
  - Patient is **not** receiving Soliris in combination with **any** of the following:
    - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]; **or**
    - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab)]; **or**

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

and

- Reauthorization will be for no more than 12 months

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1300	Injection, eculizumab, 10 mg
J1303	Injection, ravulizumab-cwvz, 10 mg

Diagnosis Code	Description
D59.30	Hemolytic-uremic syndrome, unspecified
D59.32	Hereditary hemolytic-uremic syndrome
D59.39	Other hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
G36.0	Neuromyelitis optica [Devic]
G70.00	Myasthenia gravis without (acute) exacerbation

Background

Eculizumab and ravulizumab are monoclonal antibodies that bind with high affinity to complement protein C5, which inhibits its cleavage to C5a and C5b and prevents the generation of the terminal complement complex C5b9. In those patients with paroxysmal nocturnal hemoglobinuria (PNH), eculizumab and ravulizumab inhibit terminal complement mediated intravascular hemolysis.[1,12] In patients with atypical hemolytic uremic syndrome (aHUS), impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy. The precise mechanism by which eculizumab and ravulizumab exert their therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.[1-3,12]

Clinical Evidence

Proven

Atypical Hemolytic Uremic Syndrome (aHUS)

Ravulizumab is indicated for the treatment of atypical hemolytic uremic syndrome (aHUS).[12,38]

Eculizumab is indicated for the treatment of atypical hemolytic uremic syndrome (aHUS).[1,14,15,39]

Rondeau et al. evaluated the efficacy and safety of ravulizumab for the treatment of atypical hemolytic uremic syndrome in adults.[38] In this global, phase 3, single arm study in complement inhibitor-naïve adults (18 years and older) who fulfilled diagnostic criteria for atypical hemolytic uremic syndrome, enrolled patients received ravulizumab through a 26-week initial evaluation period. Patients were required to have a platelet count ≤ 50 x 109 /L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis. A total of 56 patients with aHUS were evaluated for efficacy. The primary endpoint was complete thrombotic microangiopathy response defined as normalization of platelet count and lactate dehydrogenase and 25% or more improvement in serum creatinine. The efficacy evaluation was based on Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet each Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Secondary endpoints included changes in hematologic variables and renal function. Safety was also evaluated. Ravulizumab treatment resulted in an immediate, complete, and sustained C5 inhibition in all patients. Complete thrombotic microangiopathy response was achieved in 53.6% of patients.

The median duration of Complete TMA Response was 7.97 months (range: 2.52 to 16.69 months). Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). Normalization of platelet count, lactate dehydrogenase and 25% or more improvement in serum creatinine was achieved in 83.9%, 76.8% and 58.9% of patients, respectively. Improvement in estimated glomerular filtration rate by one or more stage was achieved in 68.1% of patients by day 183. An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 × 109 /L at baseline to 240.34 ×109 /L at Day 8 and remaining above 227 × 109 /L at all subsequent visits in the Initial Evaluation Period (26 weeks). Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. The mean eGFR (+/- SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. In patients with Complete TMA Response, renal function continued to improve after the Complete TMA Response was achieved. Seventeen of the 29 patients (59%) who required dialysis at study entry discontinued dialysis by the end of the available follow-up and 6 of 27 (22%) patients were off dialysis at baseline were on dialysis at last available follow-up. No unexpected adverse events were reported across a safety analysis set of 58 patients. Four deaths occurred (three within one month of study initiation, including one in a patient excluded based on eligibility criteria after the first dose) with none considered treatment-related by the study investigator.

Five single-arm studies [four prospective: C08-002A/B (NCT00844545 and NCT00844844), C08- 003A/B (NCT00838513 and NCT00844428), C10-003 (NCT01193348), and C10-004 (NCT01194973); and one retrospective: C09-001r (NCT01770951)] evaluated the safety and efficacy of Soliris for the treatment of aHUS.[1] Legendre et al. conducted two prospective phase 2 trials (NCT00844545 [adults] and NCT00844844 [adolescents]; NCT00838513 [adults] and NCT00844428 [adolescents]) in which patients with atypical hemolytic-uremic syndrome who were 12 years of age or older received eculizumab for 26 weeks and during long-term extension phases.[39] Patients with low platelet counts and renal damage (in trial 1) and those with renal damage but no decrease in the platelet count of more than 25% for at least 8 weeks during plasma exchange or infusion (in trial 2) were recruited. The primary end points included a change in the platelet count (in trial 1) and thrombotic microangiopathy event-free status (no decrease in the platelet count of > 25%, no plasma exchange or infusion, and no initiation of dialysis) (in trial 2). A total of 37 patients (17 in trial 1 and 20 in trial 2) received eculizumab for a median of 64 and 62 weeks, respectively. Eculizumab resulted in increases in the platelet count; in trial 1, the mean increase in the count from baseline to week 26 was 73×10(9) per liter ($p < 0.001$). In trial 2, 80% of the patients had thrombotic microangiopathy event-free status. Eculizumab was associated with significant improvement in all secondary end points, with continuous, time-dependent increases in the estimated glomerular filtration rate (GFR). In trial 1, dialysis was discontinued in 4 of 5 patients. Earlier intervention with eculizumab was associated with significantly greater improvement in the estimated GFR. Eculizumab was also associated with improvement in health-related quality of life. In trial 1, all patients had at least one serious adverse event; four events were reported as being possibly related to eculizumab, one of which was considered severe (hypertension in a patient with a history of this disorder). In trial 2, a total of 10 patients (50%) had serious adverse events, of whom 2 patients had a total of three serious adverse events that were possibly or probably drug-related (peritonitis, influenza, and vein disorder). One patient had one drug-related serious adverse event and the other patient had two such events. No deaths were reported in either trial. All serious adverse events possibly or probably related to eculizumab resolved without interruption of treatment. No cumulative toxicity of therapy or serious infection-related adverse events, including meningococcal infections, were observed through the extension period.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Ravulizumab is indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).[12,14,15]

Eculizumab is indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).[1]

The safety and efficacy of Ultomiris in adult patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority Phase 3 studies: PNH Study 301 and PNH Study 302. Study 301 enrolled patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.[12] Lee et al. evaluated the safety and efficacy of Ultomiris in PNH Study 301, a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 246 patients naïve to complement inhibitor treatment prior to study entry.[14] Patients with lactate dehydrogenase (LDH) ≥ 1.5 times the upper limit of normal and at least 1 PNH symptom were randomized 1:1 to receive ravulizumab or eculizumab for 183 days. Ultomiris was dosed intravenously in accordance with a weight-based dosing schedule (4 infusions of ULTOMIRIS over 26 weeks). Eculizumab was administered on Days 1, 8, 15, and 22, followed by maintenance treatment with 900 mg of eculizumab on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment, according to the approved dosing regimen of eculizumab which was the standard-of-care for PNH at the time of the studies. Ninety-eight percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (85%), hemoglobinuria (63%), history of aplastic anemia (32%), history of renal failure (12%), myelodysplastic syndrome (5%), pregnancy complications (3%), and other (16%). Patients either were vaccinated

against meningococcal infection prior to or at the time of initiating treatment with ULTOMIRIS or eculizumab or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. Prophylactic treatment with appropriate antibiotics beyond 2 weeks after vaccination was at the discretion of the provider. Coprimary efficacy end points were proportion of patients remaining transfusion-free and LDH normalization. Secondary end points were percent change from baseline in LDH, change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue score, proportion of patients with breakthrough hemolysis, stabilized hemoglobin, and change in serum free C5. Ravulizumab was noninferior to eculizumab for both coprimary and all key secondary end points (Pinf < .0001): transfusion avoidance (73.6% vs 66.1%; difference of 6.8% [95% confidence interval (CI), −4.66, 18.14]), LDH normalization (53.6% vs 49.4%; odds ratio, 1.19 [0.80, 1.77]), percent reduction in LDH (−76.8% vs −76.0%; difference [95% CI], −0.83% [−5.21, 3.56]), change in FACIT-Fatigue score (7.07 vs 6.40; difference [95% CI], 0.67 [−1.21, 2.55]), breakthrough hemolysis (4.0% vs 10.7%; difference [95% CI], −6.7% [−14.21, 0.18]), and stabilized hemoglobin (68.0% vs 64.5%; difference [95% CI], 2.9 [−8.80, 14.64]). There was no observable difference in fatigue between Ultomiris and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. The most frequently reported AE was headache (36.0% and 33.1% in the ravulizumab and eculizumab groups, respectively). Twenty patients experienced serious AEs (11 ravulizumab and 9 eculizumab patients); pyrexia was the only serious AE reported in > 1 patient (1 ravulizumab patient and 2 eculizumab patients). No cases of meningococcal infections, Aspergillus infections, or sepsis were reported. Other serious infections occurred in 2 patients (1.6%) in the ravulizumab group and 4 (3.3%) in the eculizumab group. Serious infections observed in patients treated with ravulizumab included leptospirosis and systemic infection (causative agents not identified); serious infections observed in patients treated with eculizumab included limb abscess, cellulitis, infection, pneumonia, and viral upper respiratory tract infection (causative agents not identified).

Hillmen et al. evaluated the long-term safety and efficacy of continuous administration of eculizumab in 195 patients with paroxysmal nocturnal hemoglobinuria (PNH) over 66 months.[2] Patients previously enrolled in the Phase II pilot study and its extensions, the Phase III TRIUMPH (Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria) study (NCT00122330), or the Phase III SHEPHERD (Safety in Hemolytic PNH Patients Treated With Eculizumab: A Multi-Center Open-Label Research Design) study (NCT00130000) were eligible to participate. All patients had a minimum of 10% PNH red blood cells at enrolment in the parent trials and were vaccinated with a meningococcal vaccine at least 14 days prior to the first eculizumab infusion in the parent studies. Efficacy assessments were performed at least every 2 weeks from the time of initiation of eculizumab therapy in the parent study. Efficacy endpoints included patient survival degree of hemolysis, thrombotic events (TE), mean change from baseline in hemoglobin and the number of units of transfused packed red blood cells (PRBCs) administered. Assessments of renal function were performed over the duration of the study by determining the CKD stage using formulas for estimated glomerular filtration rate (GFR). Safety was assessed through monitoring of adverse events (AEs), clinical laboratory tests and vital signs. Four patient deaths were reported, all unrelated to treatment, resulting in a 3-year survival estimate of 97.6%. All patients showed a reduction in lactate dehydrogenase levels, which was sustained over the course of treatment (median reduction of 86.9% at 36 months). The incidence of reported TEs decreased by 81.8%, with 96.4% of patients remaining free of TEs. Researchers observed a time-dependent improvement in renal function: 93.1% of patients exhibited improvement or stabilization in CKD score at 36 months. Transfusion independence increased by 90.0% from baseline, with the number of red blood cell units transfused decreasing by 54.7%. The median treatment duration was 30.3 months with a maximum duration of 66 months. Eculizumab was well tolerated, with no evidence of cumulative toxicity and a decreasing occurrence of adverse events over time. Very few patients discontinued treatment. Researchers concluded that long-term treatment with eculizumab resulted in sustained improvement in patient outcomes by rapidly reducing hemolysis and significantly reducing the frequency of severe and life-threatening morbidities, such as TEs and CKD, and thus, improving patient survival.

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) level, 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.[34]

Generalized Myasthenia Gravis

Ravulizumab is indicated for the treatment of generalized myasthenia gravis.[36]

Eculizumab is indicated for the treatment of generalized myasthenia gravis.[1]

Vu et al. completed a phase 3, randomized, double-blind, placebo-controlled, multicenter study (CHAMPION MG) that evaluated the safety and efficacy of ravulizumab in complement-inhibitor-naïve patients 18 years of age and older, with a confirmed diagnosis of generalized myasthenia gravis.[37,38] Patients were required to be classified by the Myasthenia Gravis Foundation of America as Class II to IV at screening, and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale ≥ 6 at screening and randomization, and vaccination against Neisseria meningitidis. One hundred seventy-five patients were randomized to receive either placebo (n = 89), or ravulizumab (n = 86). Ravulizumab dosing was based on the patient's body weight: patient weight ≥ 40 kg to < 60 kg: 2400 mg loading dose, 3000 mg maintenance dose; weight ≥ 60 kg to < 100 kg: 2700 mg loading dose, 3300 mg maintenance dose; weight ≥ 100 kg, 3000 mg loading dose, 3600 mg maintenance dose. Patients received an initial loading dose of ravulizumab (2400, 2700, or 3000 mg) or placebo at baseline (day 1), followed by maintenance doses of ravulizumab (3000, 3300, or 3600 mg) or placebo on day 15 (week 2) and every 8 weeks thereafter. The primary outcome measure was the change in MG-ADL total score from baseline at week 26 as compared to placebo. A clinical response in MG-ADL was defined as at least a 3-point improvement. In this study, the primary end point (change from baseline in MG-ADL total score at 26 weeks) was statistically significantly improved with ravulizumab compared with placebo (−3.1 vs. −1.4; $p < 0.001$). There were two deaths in the ravulizumab group: one due to Covid-19 and one attributable to cerebral hemorrhage. There were no cases of meningococcal infection. No notable differences in adverse events between the two groups were observed. The most frequent adverse event was headache, experienced by 16 patients (19%) in the ravulizumab group and 23 (26%) in the placebo group. The other most common adverse reactions (≥ 10%) were diarrhea and upper respiratory tract infection. Serious adverse events were reported for 20 patients (23%) in the ravulizumab group and 14 (16%) in the placebo group. The most frequent serious adverse events were related to worsening of MG (one patient receiving ravulizumab and three receiving placebo) and Covid-19 (two receiving ravulizumab and one receiving placebo). A treatment effect, including improvement in clinical and functional outcomes, was observed within the first week of treatment and sustained throughout the 26-week randomized trial period. The difference between ravulizumab and placebo was statistically significant for the primary end point, despite a notable placebo effect. The authors stated that the influence of the Covid-19 pandemic was an important limitation to this study. Although mitigation measures allowed the trial to continue collecting data per trial design, it is undetermined how the pandemic may have affected assessments, particularly those related to health-related quality of life (HR-QoL).

Howard et al. completed a phase 3 randomized, double-blind, placebo-controlled, multi-center study (REGAIN) that assessed the efficacy and safety of eculizumab in patients 18 years of age and older, with a confirmed diagnosis of generalized myasthenia gravis.[9,11] Patients were required to be classified by the Myasthenia Gravis Foundation of America as Class II to IV at screening, and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale ≥ 6 at screening and randomization, and vaccination against Neisseria meningitidis. Patients were also to have failed at least two immunosuppressive agents, or failed at least one agent, and require chronic plasma exchange or IVIG for 12 months without symptom control. One hundred twenty-five patients were randomized to receive either placebo (n = 63), or eculizumab (n = 62): 900 mg IV weekly for 4 doses, followed by 1,200 mg IV every 2 weeks during weeks 4 through 26. Primary outcome measures included the change in total MG-ADL score and the change in MG-ADL total score from baseline at week 26 as compared to placebo. A clinical response in MG-ADL was defined as at least a 3-point improvement. The primary analysis showed no significant difference between eculizumab and placebo. In evaluating clinically meaningful response, a higher proportion of patients achieved a clinically meaningful response with eculizumab than with placebo ($p < 0.05$). No deaths or cases of meningococcal infection occurred during the study. The most common adverse events in both groups were headache and upper respiratory tract infection. Myasthenia gravis exacerbations were reported by six (10%) patients in the eculizumab group and 15 (24%) in the placebo group. Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy. The change in the MG-ADL score was not statistically significant between eculizumab and placebo, as measured by the worst-rank analysis. Eculizumab was well tolerated. The authors disclosed that the use of a worst-rank analytical approach proved to be an

important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result. The authors state that further research into the role of complement is needed.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Eculizumab is indicated for the treatment of 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 were randomly 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-of-life 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.

Unproven

Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).[1] While the few studies available demonstrate possible efficacy of eculizumab in treating Shiga toxin E. coli-related hemolytic uremic syndrome,[4-6] further studies are warranted to demonstrate that it is both safe and effective for this indication.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Soliris (eculizumab) is a complement inhibitor indicated for:[1]

- 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
- Treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive
- Treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive

Limitations of Use[1]: Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Ultomiris (ravulizumab-cwvz) is a complement inhibitor indicated for:[12]

- The treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).
- The treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).
- Treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody-positive.

Limitations of Use[12]: Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

The use of Soliris and Ultomiris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early:

- Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization 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 or Ultomiris
    - If urgent therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible
- Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if an infection is suspected

Soliris and Ultomiris are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the REMS programs, prescribers must enroll in the program. Enrollment in the Soliris REMS or Ultomiris REMS programs and additional information are available by telephone: 1-888-765-4747 or at http://www.solirisrems.com or www.ultomirisrems.com.[1,3,12,13]

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Policy History/Revision Information

Date	Summary of Changes

09/01/2024	**Coverage Rationale**
	Paroxysmal Nocturnal Hemoglobinuria (PNH)
	• Revised coverage criteria:
	  ○ Added criterion requiring the patient is not receiving Soliris or Ultomiris in combination with another complement inhibitor [e.g., Empaveli (pegcetacoplan), Fabhalta (iptacopan)]
	  ○ Removed criterion requiring:
	  ▪ Patient is < 18 years of age
	  ▪ Patient is pregnant
	Continuation of Therapy
	  ▪ Both of the following:
	  – Patient has a hemoglobin level greater than 10.5 g/dL
	  – Patient has not required red blood cell transfusions to maintain a hemoglobin level greater than 10.5 g/dL
	  ▪ Both of the following:
	  – Prescriber attests that the patient has been counseled on alternative chronic treatment options for PNH
	  – Prescriber attests that the patient has shared in decision-making on their PNH therapy plan
	Supporting Information
	• Updated *References* section to reflect the most current information
	• Archived previous policy version CSLA2024D0049R

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.