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

Policy Number: CSLA2021D0049LK
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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 to the following complement inhibitor drug products:

- Soliris (eculizumab)
- Ultomiris (ravulizumab-cwvz)

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)
    - 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 are dosed according to the U.S. 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 6 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 are dosed according to the U.S. 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
    - 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 U.S. FDA labeled dosing for PNH; **and**
  - Prescribed by, or in consultation with, a hematologist or oncologist; **and**
  - Initial authorization will be for no more than 6 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 U.S. FDA labeled dosing for PNH; **and**
  - Prescribed by, or in consultation with, a hematologist or oncologist; **and**
  - Reauthorization will be for no more than 12 months

Soliris is proven and medically necessary for the treatment of generalized myasthenia gravis when all of the following criteria are met:[1,9,11]

- Initial Therapy:
  - 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:
    - Patient has not failed a previous course of Soliris therapy; **and**
    - Positive serologic test for anti-AChR antibodies; **and**
    - **One** of the following:
      - History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation
      - History of positive anticholinesterase test, e.g., edrophonium chloride test
      - Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating neurologist;

      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-specific Activities of Daily Living scale (MG-ADL) total score ≥ 6 at initiation of therapy;

    and
  - **Both** of the following:
    - History of failure of at least **two** immunosuppressive agents over the course of at least 12 months (e.g., azathioprine, methotrexate, cyclosporine, mycophenylate, etc.); **and**
    - Patient has required **two** or more courses of plasmapheresis/plasma exchanges and/or intravenous immune globulin for at least 12 months without symptom control;

    and
  - Patient is currently on a stable dose (at least 2 months) of immunosuppressive therapy; **and**

- Soliris is initiated and titrated according to the U.S. FDA labeled dosing for gMG: up to a maximum of 1200 mg every 2 weeks; **and**
- Prescribed by, or in consultation with, a neurologist; **and**
- Initial authorization will be for no more than 6 months

- Continuation of Therapy:
  - Patient has previously been treated with Soliris; **and**
  - 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:
    - Improvement and/or maintenance of at least a 3 point improvement (reduction in score) in the MG-ADL score from pre-treatment baseline
    - Reduction in signs and symptoms of myasthenia gravis
    - Maintenance, reduction, or discontinuation of dose(s) of baseline immunosuppressive therapy (IST) prior to starting *Soliris (***Note**: Add on, dose escalation of IST, or additional rescue therapy from baseline to treat myasthenia gravis or exacerbation of symptoms while on Soliris therapy will be considered as treatment failure);

    and
  - Soliris is dosed according to the U.S. FDA labeled dosing for gMG: up to a maximum of 1200 mg every 2 weeks; **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:

- Initial Therapy:
  - 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:[22-25]
    - Past medical history of **one** of the following:[25]
      - 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;

      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
    - 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 U.S. FDA labeled dosing for NMOSD, up to a maximum of 1200 mg every 2 weeks; **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.]

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

      and

    - Initial authorization will be for no more than 6 months
- Continuation of Therapy:
    - Patient has previously been treated with Soliris; **and**
    - 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:
        - Reduction in the number and/or severity of relapses or signs and symptoms of NMOSD
        - 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 U.S. FDA labeled dosing for NMOSD: up to a maximum of 1200 mg every 2 weeks; **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.]
        - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab)]
        - Rituximab;

      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
D59.3	Hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
G36.0	Neuromyelitis optica [Devic]
G70.00	Myasthenia gravis without (acute) exacerbation

Maximum Dosage Requirements

Maximum Allowed Quantities by HCPCS Units

This section provides information about the maximum dosage per administration for omalizumab administered by a medical professional.

Medication Name		Diagnosis	Maximum Dosage per Administration	HCPCS Code	Maximum Allowed
Brand	Generic				
Soliris	Eculizumab	aHUS	1200 mg	J1300	120 HCPCS units (10 mg per unit)
Soliris	Eculizumab	MG/NMOSD	1200 mg	J1300	120 HCPCS units (10 mg per unit)
Soliris	Eculizumab	PNH	900 mg	J1300	90 HCPCS units (10 mg per unit)
Ultomiris	ravulizumab-cwvz		3,600 mg total dose	J1303	360 HCPCS units (10 mg per unit)

Maximum Allowed Quantities by National Drug Code (NDC) Units

The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDC's for each drug product and is subject to change.

Medication Name		Diagnosis	How Supplied	National Drug Code	Maximum Allowed
Brand	Generic				
Soliris	Eculizumab	aHUS	300 mg vials	25682-0001-01	4 vials/120 ml
Soliris	Eculizumab	MG/NMOSD	300 mg vials	25682-0001-01	4 vials/120 ml
Soliris	Eculizumab	PNH	300 mg vials	25682-0001-01	3 vials/90 ml
Ultomiris	ravulizumab-cwvz	-	300 mg/30 mL solution in vials	25682-0022-01	360 mL
			300 mg/3 mL solution in vials	25682-0025-01	36 mL
			1,100 mg/11 mL solution in vials	25682-0028-01	36 mL

Background

Eculizumab and ravulizumab are monoclonal antibodies that bind with high affinity to compliment protein C5, which inhibits its cleavage to C5a and C5b and prevents the generation of the terminal complement complex C5b-9. 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 exerts its 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]

Proven

Atypical Hemolytic Uremic Syndrome (aHUS)

Ravulizumab is indicated for the treatment of atypical hemolytic uremic syndrome (aHUS).~~paroxysmal nocturnal hemoglobinuria (aHUS)~~.[12]

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

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]

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.

Generalized Myasthenia Gravis

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

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 meningitides. 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 antiacetylcholine receptor (AchR) antibody positive
- The 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 adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

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

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
xx/01/2021	Updated clinical evidence section and FDA information. Updated references.

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.