Ultomiris (ravulizumab-cwvz) has been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Refer to the policy titled Review at Launch for New to Market Medications for additional details.

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

**I. Soliris is proven for the treatment of atypical Hemolytic Uremic Syndrome (aHUS).**

**Soliris is medically necessary when all of the following criteria are met:**

A. **Initial Therapy:**
   1. Documentation supporting the diagnosis of aHUS by ruling out both of the following:
      a. Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS);
      b. Thrombotic thrombocytopenia purpura (TTP) (e.g., rule out ADAMTS13 deficiency) and
   2. Soliris is initiated and titrated according to the US FDA labeled dosing for aHUS, up to a maximum of 1200 mg every 2 weeks; and
   3. Prescribed by or in consultation with a hematologist; and
   4. Initial authorization will be for no more than 6 months.

B. **Continuation Therapy:**
   1. Patient has previously been treated with Soliris; and
   2. Documentation demonstrating a positive clinical response from baseline (e.g., reduction of plasma exchanges, reduction of dialysis, increased platelet count, reduction of hemolysis); and
   3. Soliris is dosed according to the US FDA labeled dosing for aHUS: 1200 mg every 2 weeks; and
   4. Prescribed by or in consultation with a hematologist; and
   5. Reauthorization will be for no more than 12 months.

**II. Soliris is unproven and not medically necessary for treatment of Shiga Toxin E. Coli-related Hemolytic Uremic Syndrome (STEC-HUS).**

**III. Soliris and Ultomiris are proven for the treatment of paroxysmal Nocturnal Hemoglobinuria (PNH).**

**Soliris and Ultomiris are medically necessary when all of the following criteria are met:**

A. **Initial Therapy:**
   1. Documentation supporting the diagnosis of PNH that includes both of the following:
      a. Flow cytometry analysis confirming presence of PNH clones.
b. 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

2. Patient is treatment naive with both Soliris and Ultomiris; and
3. Soliris or Ultomiris are dosed according to the US FDA labeled dosing for PNH; and
4. Prescribed by or in consultation with a hematologist or oncologist; and
5. Initial authorization will be for no more than 6 months.

B. Continuation Therapy:
1. Patient has previously been treated with Soliris or Ultomiris; and
2. 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
3. Soliris or Ultomiris are dosed according to the US FDA labeled dosing for PNH; and
4. Prescribed by or in consultation with a hematologist or oncologist; and
5. Reauthorization will be for no more than 12 months.

IV. Soliris is proven for the treatment of generalized Myasthenia Gravis. 1,9,11
Soliris is medically necessary when all of the following criteria are met:

A. Initial therapy:
1. 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:
   a. Patient has not failed a previous course of Soliris therapy; and
   b. Positive serologic test for anti-AChR antibodies; and
   c. One of the following:
      i. History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation
      ii. History of positive anticholinesterase test, e.g., edrophonium chloride test
      iii. Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating neurologist
      and
   d. Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II, III, or IV at initiation of therapy; and
   e. Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II, III, or IV at initiation of therapy

and

2. Both of the following:
   a. History of failure of at least two immunosuppressive agent over the course of at least 12 months [e.g., azathioprine, methotrexate, cyclosporine, mycophenolate, etc.]; and
   b. Patient has required 2 or more courses of plasmapheresis/plasma exchanges and/or intravenous immune globulin for at least 12 months without symptom control

and

3. Patient is currently on a stable dose (at least 2 months) of immunosuppressive therapy; and
4. Soliris is initiated and titrated according to the US FDA labeled dosing for gMG, up to a maximum of 1200 mg every 2 weeks; and
5. Prescribed by or in consultation with a Neurologist; and
6. Initial authorization will be for no more than 6 months.

B. Continuation therapy:
1. Patient has previously been treated with Soliris; and
2. 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:
   a. Improvement and/or maintenance of at least a 3 point improvement (reduction in score) in the MG-ADL score from pre-treatment baseline.
   b. Reduction in signs and symptoms of myasthenia gravis
   c. 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

3. Soliris is dosed according to the US FDA labeled dosing for gMG: up to a maximum of 1200 mg every 2 weeks; and
4. Prescribed by or in consultation with a Neurologist; and
5. Reauthorization will be for no more than 12 months.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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.

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 the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

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

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 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 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

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 the member specific benefit plan document 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 Coverage Determination Guidelines may apply.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1300</td>
<td>Injection, eculizumab, 10 mg</td>
</tr>
<tr>
<td>J3590</td>
<td>Unclassified biologics (to be used for ravulizumab)</td>
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</table>

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D59.3</td>
<td>Hemolytic-uremic syndrome</td>
</tr>
</tbody>
</table>
ICD-10 Diagnosis Code | Description
--- | ---
D59.5 | Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
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.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Diagnosis</th>
<th>Maximum Dosage per Administration</th>
<th>HCPCS Code</th>
<th>Maximum Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris</td>
<td>eculizumab</td>
<td>aHUS</td>
<td>1200 mg</td>
<td>J1300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myasthenia Gravis</td>
<td>1200 mg</td>
<td>J1300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PNH</td>
<td>900 mg</td>
<td>J1300</td>
</tr>
</tbody>
</table>

**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 NDCs for each drug product and is subject to change.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Diagnosis</th>
<th>How Supplied</th>
<th>National Drug Code</th>
<th>Maximum Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris</td>
<td>eculizumab</td>
<td>aHUS</td>
<td>300 mg vials</td>
<td>25682-0001-01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myasthenia Gravis</td>
<td>300 mg vials</td>
<td>25682-0001-01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PNH</td>
<td>300 mg vials</td>
<td>25682-0001-01</td>
</tr>
</tbody>
</table>

**BENEFIT CONSIDERATIONS**

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

**Additional Information**: Clinical coverage in this policy addresses the drug only. It does not address coverage for drug administration in a hospital outpatient department. Please refer to the member specific benefit plan document and the [Specialty Medication Administration - Site of Care Review Guidelines](#) for more information. The member specific benefit plan document determines coverage.

**CLINICAL EVIDENCE**

**Proven**

**Atypical Hemolytic Uremic Syndrome (aHUS)**

Eculizumab is indicated for the treatment of atypical hemolytic uremic syndrome (aHUS).\(^1,14,15\)

**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.

**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.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) that specifically addresses eculizumab (Soliris®) or ravulizumab-cwvz (Ultomiris™). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the [Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals](https://www.cms.gov/medicare/coverage-analysis/bp-manual/bp-chapter15.html) (Accessed January 3, 2019)

**REFERENCES**


POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tr>
<td>05/01/2019</td>
<td>Off cycle review. Revised coverage rationale for PNH. Approved by the National Pharmacy and Therapeutics Committee 04/17/2019. Policy 2019D0049G archived.</td>
</tr>
<tr>
<td>03/01/2019</td>
<td>Off cycle review. Changed policy name to Complement Inhibitors. Relocated Instructions for Use and Benefit Considerations sections. Added Ultomiris (ravulizumab) to the policy. Updated FDA statement, background, clinical evidence, references. Approved by the National Pharmacy and Therapeutics Committee 02/15/2019. Policy 2018D0049F archived.</td>
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<tr>
<td>08/01/2018</td>
<td>Annual Review with minor revision of the Coverage Rationale. Updated CMS statement and references. Approved by the National Pharmacy and Therapeutics Committee 07/18/2018. Policy 2018D0049E archived.</td>
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<td>Date</td>
<td>Action/Description</td>
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</table>
| 01/01/2018 | • Off cycle review. Revised coverage criteria for all indications. Updated FDA statement, background, clinical evidence, references. Approved by the National Pharmacy and Therapeutics Committee 12/20/2017.  
  • Annual review. Added coverage criteria for generalized myasthenia gravis. Added medical necessity criteria for aHUS and PNH. Updated FDA statement, background, and clinical evidence. Updated CMS statement and references. Approved by the National Pharmacy and Therapeutics Committee 07/28/2017.  
  • Policy 2016D0049D archived.                                                                                                                                 |
| 08/01/2017 | Moved policy to new template.                                                                                                                                                                                     |
| 07/01/2016 | Annual review with no changes to Coverage Rationale. Updated CMS statement and references. Approved by the National Pharmacy and Therapeutics Committee 05/20/2016. Policy 2015D0049C archived.                                           |
| 10/01/2015 | Updated Applicable Codes for ICD-10 transition. Policy 2015D0049B archived.                                                                                                                                       |
| 08/01/2015 | Annual review with no change to Coverage Rationale. Updated CMS and references. Approved by the National Pharmacy and Therapeutics Committee 05/20/2015. Policy 2014D0049A archived.                                              |
| 10/01/2014 | Annual review with no change to Coverage Rationale. Updated CMS and references. Approved by the National Pharmacy and Therapeutics Committee 05/21/2014                                                                 |
| 10/01/2013 | New policy 2013D0049A. Approved by the National Pharmacy and Therapeutics Committee 07/09/2013.                                                                                                                  |

**INSTRUCTIONS FOR USE**

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. 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.