Clinical Policy: Ravulizumab-cwvz (Ultomiris)

Reference Number: ERX.SPA.326
Effective Date: 06.01.19
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Ravulizumab-cwvz (Ultomiris®) is a complement inhibitor.

FDA Approved Indication(s)
Ultomiris is indicated for the treatment of:

- Adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH)
- Adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA)

Limitation(s) of use: Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Ultomiris is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all)**:**

1. Diagnosis of PNH;
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 1 month;
4. Flow cytometry shows detectable GPI-deficient hematopoietic clones or ≥ 5% PNH cells;
5. Member meets one of the following (a or b):
   a. History of ≥ 1 red blood cell transfusion in the past 24 months and (i or ii):
      i. Documentation of hemoglobin < 7 g/dL in members without anemia symptoms;
      ii. Documentation of hemoglobin < 9 g/dL in members with anemia symptoms;
   b. History of thrombosis;
6. Ultomiris is not prescribed concurrently with Soliris®;
7. Dose does not exceed the following (a, b, and c):
   a. Loading dose on Day 1:
      i. Weight ≥ 5 to < 10 kg: 600 mg;
      ii. Weight ≥ 10 to < 20 kg: 600 mg;
      iii. Weight ≥ 20 to < 30 kg: 900 mg;
      iv. Weight ≥ 30 to < 40 kg: 1,200 mg;
      v. Weight ≥ 40 to < 60 kg: 2,400 mg;
      vi. Weight ≥ 60 to < 100 kg: 2,700 mg;
      vii. Weight ≥ 100 kg: 3,000 mg;
   b. If member is switching therapy from Soliris, administration of the loading dose should occur 2 weeks after the last Soliris infusion;

c. Maintenance dose on Day 15 and at the specified frequency thereafter:
   i. Weight ≥ 5 to < 10 kg: 300 mg every 4 weeks;
   ii. Weight ≥ 10 to < 20 kg: 600 mg every 4 weeks;
   iii. Weight ≥ 20 to < 30 kg: 2,100 mg every 8 weeks;
   iv. Weight ≥ 30 to < 40 kg: 2,700 mg every 8 weeks;
   v. Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;
   vi. Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;
   vii. Weight ≥ 100 kg: 3,600 mg every 8 weeks.

Approval duration: 6 months

B. Atypical Hemolytic Uremic Syndrome (must meet all)**:**
1. Diagnosis of aHUS (i.e., complement-mediated HUS);
2. Prescribed by or in consultation with a hematologist or nephrologist;
3. Age ≥ 1 month;
4. Member has signs of TMA as evidenced by all of the following (a, b, and c):
   a. Platelet count ≤ 150 x 10^9/L;
   b. Hemolysis such as an elevation in serum lactate dehydrogenase (LDH);
   c. Serum creatinine above the upper limits of normal or member requires dialysis;
5. Documentation that member does not have either of the following:
   a. A disintegrin and metalloproteinase with thombospondin type 1 motif, member 13 (ADAMTS13) deficiency;
   b. STEC-HUS;
6. Ultomiris is not prescribed concurrently with Soliris;
7. Dose does not exceed the following (a, b, and c):
   a. Loading dose on Day 1:
      i. Weight ≥ 5 to < 10 kg: 600 mg;
      ii. Weight ≥ 10 to < 20 kg: 600 mg;
      iii. Weight ≥ 20 to < 30 kg: 900 mg;
      iv. Weight ≥ 30 to < 40 kg: 1,200 mg;
      v. Weight ≥ 40 to < 60 kg: 2,400 mg;
      vi. Weight ≥ 60 to < 100 kg: 2,700 mg;
      vii. Weight ≥ 100 kg: 3,000 mg;
   b. If member is switching therapy from Soliris, administration of the loading dose should occur 2 weeks after the last Soliris infusion;
   c. Maintenance dose on Day 15 and at the specified frequency thereafter:
      i. Weight ≥ 5 to < 10 kg: 300 mg every 4 weeks;
      ii. Weight ≥ 10 to < 20 kg: 600 mg every 4 weeks;
      iii. Weight ≥ 20 to < 30 kg: 2,100 mg every 8 weeks;
      iv. Weight ≥ 30 to < 40 kg: 2,700 mg every 8 weeks;
      v. Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;
      vi. Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;
      vii. Weight ≥ 100 kg: 3,600 mg every 8 weeks.

Approval duration: 6 months

C. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters (a or b):
   a. PNH:

i. Improved measures of intravascular hemolysis (e.g., normalization of LDH);
ii. Reduced need for red blood cell transfusions;
iii. Increased or stabilization of hemoglobin levels;
iv. Less fatigue;
v. Improved health-related quality of life;
vi. Fewer thrombotic events;

b. aHUS:
i. Improved measures of intravascular hemolysis (e.g., normalization of LDH);
ii. Increased or stabilized platelet counts;
iii. Improved or stabilized serum creatinine or estimated glomerular filtration rate (eGFR);
iv. Reduced need for dialysis;

3. Ultomiris is not prescribed concurrently with Soliris;
4. If request is for a dose increase, new dose does not exceed one of the following:
a. Weight ≥ 5 to < 10 kg: 300 mg every 4 weeks;
b. Weight ≥ 10 to < 20 kg: 600 mg every 4 weeks;
c. Weight ≥ 20 to < 30 kg: 2,100 mg every 8 weeks;
d. Weight ≥ 30 to < 40 kg: 2,700 mg every 8 weeks;
e. Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;
f. Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;
g. Weight ≥ 100 kg: 3,600 mg every 8 weeks.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ADAMTS13: a disintegrin and metalloproteinase with thombospondin type 1 motif, member 13
aHUS: atypical hemolytic uremic syndrome
FDA: Food and Drug Administration
GPI: glycosyl phosphatidylinositol
LDH: lactate dehydrogenase
PNH: paroxysmal nocturnal hemoglobinuria
STEC-HUS: Shiga toxin E. coli related hemolytic uremic syndrome
TMA: thrombotic microangiopathy

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): patients with unresolved *Neisseria Meningitidis* infection; patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Ultomiris treatment outweigh the risks of developing a meningococcal infection
- Boxed warning(s): serious meningococcal infections

Appendix D: General Information

- Ultomiris is only available through a REMS (Risk Evaluation and Mitigation Strategy) program due to the risk of life-threatening and fatal meningococcal infection. Patients should be vaccinated with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of Ultomiris and revaccinated according to current medical guidelines for vaccine use. Patients should be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics if necessary.
- Examples of symptoms of anemia include but are not limited to: dizziness or lightheadedness, fatigue, pale or yellowish skin, shortness of breath, chest pain, cold hands and feet, and headache.
- Ultomiris is a humanized monoclonal antibody to complement component C5 that was engineered from Soliris. It is virtually identical to Soliris but has a longer half-life that allows for less frequent dosing intervals.

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>PNH, aHUS</td><td>
<table>
<tr><th>Body Weight Range (kg)</th><th>Loading Dose (mg)</th><th>Maintenance Dose (mg)</th></tr>
<tr><td>≥ 5 to < 10</td><td>600</td><td>300 every 4 weeks</td></tr>
<tr><td>≥ 10 to < 20</td><td>600</td><td>600 every 4 weeks</td></tr>
<tr><td>≥ 20 to < 30</td><td>900</td><td>2,100 every 8 weeks</td></tr>
<tr><td>≥ 30 to < 40</td><td>1,200</td><td>2,700 every 8 weeks</td></tr>
<tr><td>≥ 40 to < 60</td><td>2,400</td><td>3,000 every 8 weeks</td></tr>
<tr><td>≥ 60 to < 100</td><td>2,700</td><td>3,300 every 8 weeks</td></tr>
<tr><td>≥ 100</td><td>3,000</td><td>3,600 every 8 weeks</td></tr>
</table>
Day 1: Loading dose IV
Day 15 and thereafter: Maintenance dose IV
</td><td>3,600 mg/
8 weeks</td></tr>
</table>

**For patients switching from eculizumab to Ultomiris, administer the loading dose of Ultomiris IV 2 weeks after the last eculizumab infusion, and then administer maintenance doses IV once at the specified frequency, starting 2 weeks after loading dose administration.*

VI. Product Availability

Single-dose vials: 300 mg/30 mL, 300 mg/3 mL, 1,100 mg/11 mL

VII. References

1. Ultomiris Prescribing Information. Boston, MA: Alexion Pharmaceutcals, Inc.; June 2021. Available at: www.ultomiris.com. Accessed June 23, 2021.
2. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 2005; 106(12):3699-3709. doi:10.1182/blood-2005-04-1717.
3. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016; 31: 15-39.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	02.19.19	05.19
1Q 2020 annual review: criteria added for new FDA indication: aHUS; references reviewed and updated.	11.26.19	02.20
1Q 2021 annual review: added requirement against concurrent use with Soliris; RT4: added new strength vials- 300 mg/3 mL and 1,100 mg/11 mL; references reviewed and updated.	10.20.20	02.21
RT4: updated age and dosing requirements for PNH per FDA pediatric expansion (from age at least 18 years to age at least 1 month).	06.23.21	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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