Clinical Policy: Ravulizumab-cwvz (Ultomiris)

Reference Number: LA.PHAR.415
Effective Date:
Last Review Date: ~~03.21~~02.22 Coding Implications
Line of Business: 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 patients 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
Prior authorization is required. Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections 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 ~~≥ 18 years~~1 month;
4. Flow cytometry shows detectable glycosylphosphatidylinositol (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 Empaveli™ or Soliris®;
7. Dose does not exceed the following (a, b, and c):
   a. Loading dose on Day 1 ~~(i, ii, or iii)~~:

Formatted: List Paragraph, Bulleted + Level: 1 + Aligned at: 0" + Indent at: 0.25"

Commented [BJ1]: PI update June 2021 to include pediatric patients 1 month or older. Criteria should reflect this change along with all other statements concerning age and dosing.

Commented [ACE2R1]: Criteria was updated based on current PI update to the drug.

Formatted: Indent: Left: 1.25", No bullets or numbering

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;
~~i.~~v. Weight ≥ 40 to < 60 kg: 2,400 mg;
~~ii.~~vi. Weight ≥ 60 to < 100 kg: 2,700 mg;
~~iii.~~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;

b.

~~c.~~ Maintenance dose on Day 15 and ~~every 8 weeks~~at the specified frequency thereafter: ~~(i, ii, or iii):~~

c.

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.

~~i. Weight ≥ 40 to < 60 kg: 3,000 mg;~~
~~ii. Weight ≥ 60 to < 100 kg: 3,300 mg;~~
~~iii. Weight ≥ 100 kg: 3,600 mg.~~

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;

Formatted: List Paragraph, Indent: Left: 0.75", Numbered + Level: 2 + Numbering Style: a, b, c, … + Start at: 1 + Alignment: Left + Aligned at: 1.5" + Indent at: 1.75"

Formatted: Numbered + Level: 1 + Numbering Style: i, ii, iii, … + Start at: 1 + Alignment: Right + Aligned at: 1" + Indent at: 1.25"

Formatted: Normal, No bullets or numbering, Tab stops: 1.5", Left + Not at 1"

Formatted: Normal, No bullets or numbering, Tab stops: Not at 1"

Formatted: Font: Bold

Formatted: Indent: Left: 0"

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 the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all):

1. Currently receiving medication via Louisiana Healthcare Connections benefit 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 (a or b);
a. PNH: Empaveli or Soliris;
~~3.~~b.aHUS: Soliris.
4. If request is for a dose increase, new dose does not exceed one of the following ~~(a or b)~~:

Formatted

~~a.PNH:~~
~~i. Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;~~
~~ii. Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;~~
~~iii. Weight ≥ 100 kg: 3,600 mg every 8 weeks;~~

~~b. aHUS:~~

~~i.~~a. Weight ≥ 5 to < 10 kg: 300 mg every 4 weeks;
~~ii.~~b. Weight ≥ 10 to < 20 kg: 600 mg every 4 weeks;
~~iii.~~c. Weight ≥ 20 to < 30 kg: 2,100 mg every 8 weeks;
~~iv.~~d. Weight ≥ 30 to < 40 kg: 2,700 mg every 8 weeks;
~~v.~~e. Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;
~~vi.~~f. Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;
~~vii.~~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 Louisiana Healthcare Connections benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.

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 – LA.PMN.53 for Medicaid or evidence of coverage documents.

~~A.~~**B.** Amyotrophic lateral sclerosis.

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

Formatted: Numbered + Level: 1 + Numbering Style: a, b, c, ... + Start at: 1 + Alignment: Left + Aligned at: 1.63" + Indent at: 1.75"

Formatted: Numbered + Level: 1 + Numbering Style: a, b, c, ... + Start at: 1 + Alignment: Left + Aligned at: 1.63" + Indent at: 1.75"

- 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.
- In August 2021, Alexion announced it is discontinuing the global CHAMPION-ALS phase 3 clinical study of Ultomiris in adults with amyotrophic lateral sclerosis due to an interim data review showing a lack of efficacy.
-

Formatted: Indent: Left: 0.5", No bullets or numbering

V. Dosage and Administration

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

**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 Pharmaceuticals, Inc.; June 2021. Available at: www.ultomiris.com. Accessed September 15, 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.
4. AstraZeneca. Update on CHAMPION-ALS Phase III trial of Ultomiris in amyotrophic lateral sclerosis. Press release published August 20, 2021. Available at: https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-ultomiris-phase-iii-als-trial.html. Accessed September 15, 2021.
~~1. Ultomiris Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc.; October 2020. Available at: www.ultomiris.com. Accessed October 20, 2020.~~
~~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.~~

Formatted: Numbered + Level: 1 + Numbering Style: 1, 2, 3, … + Start at: 1 + Alignment: Left + Aligned at: 0" + Indent at: 0.25"
Formatted: No underline
Field Code Changed
Formatted: No underline
Field Code Changed
Formatted: No underline
Formatted: No underline

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1303	Injection, ravulizumab-cwvz, 300 mg

Reviews, Revisions, and Approvals	Date
Converted corporate to local policy	03.~~20~~21
Updated age and dosing requirements for PNH per FDA pediatric expansion (from age at least 18 years to age at least 1 month). For PNH, added requirement for no concurrent use with Empaveli; added amyotrophic lateral sclerosis to section III as an indication not covered due to lack of efficacy; references reviewed and updated.	02.22

Important Reminder

CLINICAL POLICY
Ravulizumab-cwvz

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. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom LHCC has no control or right of control. Providers are not agents or employees of LHCC.