Clinical Policy: Ravulizumab-cwvz (Ultomiris)

Reference Number: CP.PHAR.415
Effective Date: 06.01.19
Last Review Date: 02.22
Line of Business: Commercial, HIM*, Medicaid

Coding Implications
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.

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***For Health Insurance Marketplace (HIM),** if request is for pharmacy benefit, Ultomiris is non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

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)
- Adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive

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.

It is the policy of health plans affiliated with Centene Corporation® 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 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. 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. Generalized Myasthenia Gravis (must meet all):
1. Diagnosis of gMG;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥ 6 at baseline;
5. Myasthenia Gravis Foundation of America (MGFA) clinical classification of Class II to IV;
6. Member has positive serological test for anti-AChR antibodies;
7. Failure of a corticosteroid (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced;
8. Failure of a cholinesterase inhibitor (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced;
9. Failure of two immunosuppressive therapies (*see Appendix B*), unless clinically significant adverse effects are experienced or all are contraindicated;
10. Ultomiris is not prescribed concurrently with Soliris;
11. Dose does not exceed the following (a, b, and c):
    a. Loading dose on Day 1:
       i. Weight ≥ 40 to < 60 kg: 2,400 mg;
       ii. Weight ≥ 60 to < 100 kg: 2,700 mg;
       iii. 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 ≥ 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.

Approval duration: 6 months

D. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy

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

1. Currently receiving medication via Centene 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, b, or c):
   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;
   c. gMG:
      i. Improved MG-ADL assessment score as evidenced by a 2-point reduction from baseline;
3. Ultomiris is not prescribed concurrently with (a or b):
   a. PNH: Empaveli or Soliris;
   b. aHUS/gMG: Soliris;
4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. PNH/aHUS:
      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;
   b. gMG:
      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.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene 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 for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

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 policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit, or evidence of coverage documents;

B. Amyotrophic lateral sclerosis.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AChR: acetylcholine receptor
ADAMTS13: a disintegrin and metalloproteinase with thombospondin type 1 motif, member 13
aHUS: atypical hemolytic uremic syndrome
FDA: Food and Drug Administration
gMG: generalized myasthenia gravis
GPI: glycosyl phosphatidylinositol
LDH: lactate dehydrogenase
MG-ADL: Myasthenia Gravis Activities of Daily Living
MGFA: Myasthenia Gravis Foundation of America
PNH: paroxysmal nocturnal hemoglobinuria
STEC-HUS: Shiga toxin E. coli related hemolytic uremic syndrome
TMA: thrombotic microangiopathy

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Corticosteroids		
betamethasone	Oral: 0.6 to 7.2 mg PO per day	7.2 mg/day
dexamethasone	Oral: 0.75 to 9 mg/day PO	9 mg/day
methylprednisolone	Oral: 12 to 20 mg PO per day; increase as needed by 4 mg every 2-3 days until there is marked clinical improvement or to a maximum of 40 mg/day	40 mg/day
prednisone	Oral: 15 mg/day to 20 mg/day; increase by 5 mg every 2-3 days as needed. Maximum: 60 mg/day	60 mg/day
Cholinesterase Inhibitors		
pyridostigmine (Mestinon®, Regonol®)	Oral immediate-release: 600 mg daily in divided doses (range, 60-1500 mg daily in divided doses) Oral sustained release: 180-540 mg QD or BID IV or IM: 2 mg every 2-3 hours	See regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
neostigmine (Bloxiverz®)	Oral: 15 mg TID. The daily dosage should be gradually increased at intervals of 1 or more days. The usual maintenance dosage is 15-375 mg/day (average 150 mg) IM or SC: 0.5 mg based on response to therapy	See regimen
Immunosuppressants		
azathioprine (Imuran®)	Oral: 50 mg QD for 1 week, then increase gradually to 2 to 3 mg/kg/day	3 mg/kg/day
mycophenolate mofetil (Cellcept®)*	Oral: Dosage not established. 1 gram BID has been used with adjunctive corticosteroids or other non-steroidal immunosuppressive medications	2 g/day
cyclosporine (Sandimmune®)*	Oral: initial dose of cyclosporine (non-modified), 5 mg/kg/day in 2 divided doses	5 mg/kg/day
Rituxan® (rituximab), Riabni™ (rituximab-arrx), Ruxience™ (rituximab-pvvr), Truxima® (rituximab-abbs)*†	IV: 375 mg/m^2 once a week for 4 weeks; an additional 375 mg/m^2 dose may be given every 1 to 3 months afterwards	See regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*
†Prior authorization is required for rituximab products

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.

- 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.
- The MGFA classification has some subjectivity in it when it comes to distinguishing mild (Class II) from moderate (Class III) and moderate (Class III) from severe (Class IV). Furthermore, it is insensitive to change from one visit to the next.
- gMG: a 2-point reduction in MG-ADL total score is considered a clinically meaningful improvement. The scale can be accessed here: https://myasthenia.org/Portals/0/ADL.pdf

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>
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</table>
Day 1: Loading dose IV
Day 15 and thereafter: Maintenance dose IV</td><td>3,600 mg/
8 weeks</td></tr>
<tr><td>gMG</td><td>
<table>
<tr><th>Body Weight Range (kg)</th><th>Loading Dose (mg)</th><th>Maintenance Dose (mg)</th></tr>
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</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 Pharmaceuticals, Inc.; April 2022. Available at: www.ultomiris.com. Accessed June 09, 2022.
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.
5. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021; 96: 114-122.
6. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidelines for the management of myasthenia gravis. Neurology. 2016; 87: 419-425.
7. ClinicalTrials.gov. NCT03920293. Safety and efficacy study of ravulizumab in adults with generalized myasthenia gravis. Available at www.clinicaltrials.gov. Accessed June 09, 2022.

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	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: removed "TBD HIM" line of business since Ultomiris is NF for HIM while there are therapeutic alternatives on F (e.g., Soliris); added HIM-Medical Benefit; 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	
1Q 2022 annual reviewed: revised HIM-Medical Benefit to HIM line of business; 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.	09.15.21	02.22
RT4: criteria added for new FDA indication: gMG.	06.13.22	

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. The Health Plan 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. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. 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. The Health Plan 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 the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.