

Clinical Policy: Ravulizumab-cwvz (Ultomiris)

Reference Number: PA.CP.PHAR.415

Effective Date: 04/2019

Last Review Date: 07/2023

[Coding Implications](#)

[Revision Log](#)

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)
- 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 PA Health & Wellness® 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 \geq 1 month;
4. Flow cytometry shows detectable glycosylphosphatidylinositol (GPI)-deficient hematopoietic clones or \geq 5% PNH cells;
5. Member meets one of the following (a or b):
 - a. History of \geq 1 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 $<$ 10 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, c or d):
 - a. Loading dose on Day 1:
 - i. Weight \geq 5 to $<$ 10 kg: 600 mg;
 - ii. Weight \geq 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 (i or ii):
 - i. IV maintenance dose on Day 15 after IV Ultomiris loading dose (or starting 1 week after the last SC Ultomiris maintenance dose if switching from SC Ultomiris) and at the specified frequency thereafter:
 - 1) Weight ≥ 5 to < 10 kg: 300 mg every 4 weeks;
 - 2) Weight ≥ 10 to < 20 kg: 600 mg every 4 weeks;
 - 3) Weight ≥ 20 to < 30 kg: 2,100 mg every 8 weeks;
 - 4) Weight ≥ 30 to < 40 kg: 2,700 mg every 8 weeks;
 - 5) Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;
 - 6) Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;
 - 7) Weight ≥ 100 kg: 3,600 mg every 8 weeks;
 - ii. SC maintenance dose on Day 15 after IV Ultomiris loading dose (or starting 8 weeks after the last IV Ultomiris maintenance dose if switching from IV Ultomiris) and at the specified frequency thereafter:
 - 1) Age ≥ 18 years and weight ≥ 40 kg: 490 mg every week;
- d. If member has received plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg), a supplemental dose of Ultomiris may be administered within 4 hours following each PE/PP intervention or IVIg cycle (*see section V*).

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 $\leq 150 \times 10^9/L$;
 - 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 thrombospondin 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, c, and d):
 - a. IV 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 IV loading dose should occur at the time of the next scheduled Soliris dose;
- c. Maintenance dose (i or ii):
 - i. IV maintenance dose on Day 15 after IV Ultomiris loading dose s(or starting 1 week after the last SC Ultomiris maintenance dose if switching from SC Ultomiris) and at the specified frequency thereafter:
 - 1) Weight ≥ 5 to < 10 kg: 300 mg every 4 weeks;
 - 2) Weight ≥ 10 to < 20 kg: 600 mg every 4 weeks;
 - 3) Weight ≥ 20 to < 30 kg: 2,100 mg every 8 weeks;
 - 4) Weight ≥ 30 to < 40 kg: 2,700 mg every 8 weeks;
 - 5) Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;
 - 6) Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;
 - 7) Weight ≥ 100 kg: 3,600 mg every 8 weeks;
 - ii. SC maintenance dose on Day 15 after IV Ultomiris loading dose (or starting 8 weeks after the last IV Ultomiris maintenance dose if switching from IV Ultomiris) and at the specified frequency thereafter:
 - 1) Age ≥ 18 years and weight ≥ 40 kg: 490 mg every week;
- d. If member has received PE, PP, or IVIg, a supplemental dose of Ultomiris may be administered within 4 hours following each PE/PP intervention or IVIg cycle (*see section V*).

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 at least one immunosuppressive therapy (*see Appendix B*), unless clinically significant adverse effects are experienced or all are contraindicated;
- 10. Ultomiris is not prescribed concurrently with Soliris or Vyvgart[™];
- 11. Dose does not exceed the following (a, b, c, and d):
 - a. IV 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 IV loading dose should occur at the time of the next scheduled Soliris dose;
- c. IV maintenance dose on Day 15 after IV Ultomiris loading dose 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;
- d. If member has received PE, PP, or IVIg, a supplemental dose of Ultomiris may be administered within 4 hours following each PE/PP intervention or IVIg cycle (*see section V*).

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): PA.CP.PMN.53 for Medicaid.

II. Continued Therapy

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

- 1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
- 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 total score as evidenced by a 2-point reduction from baseline;
- 3. Ultomiris is not prescribed concurrently with (a, b or c):
 - a. PNH: Empaveli or Soliris;
 - b. aHUS: Soliris;
 - c. gMG: Soliris or Vyvgart;
- 4. If request is for a dose increase, new dose does not exceed one of the following (a, b, or c):

- a. PNH/aHUS (i or ii):
 - i. IV (at least 1 week must have elapsed since last dose of SC Ultomiris if switching):
 - 1. Weight ≥ 5 to < 10 kg: 300 mg every 4 weeks;
 - 2. Weight ≥ 10 to < 20 kg: 600 mg every 4 weeks;
 - 3. Weight ≥ 20 to < 30 kg: 2,100 mg every 8 weeks;
 - 4. Weight ≥ 30 to < 40 kg: 2,700 mg every 8 weeks;
 - 5. Weight ≥ 40 to < 60 kg: 3,000 mg every 8 weeks;
 - 6. Weight ≥ 60 to < 100 kg: 3,300 mg every 8 weeks;
 - 7. Weight ≥ 100 kg: 3,600 mg every 8 weeks;
 - ii. SC (at least 8 weeks must have elapsed since last maintenance dose of IV Ultomiris if switching):
 - 1. Age ≥ 18 years and weight ≥ 40 kg: 490 mg every week;
- 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;
- c. All indications: If member has received PE, PP, or IVIg, a supplemental dose of Ultomiris may be administered within 4 hours following each PE/PP intervention or IVIg cycle (*see section V*).

Approval duration: 6 months

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

- 1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

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): PA.CP.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 – PA.CP.PMN.53 for Medicaid 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 thrombospondin type 1 motif, member 13
aHUS: atypical hemolytic uremic syndrome
FDA: Food and Drug Administration

gMG: generalized myasthenia gravis
GPI: glycosyl phosphatidylinositol
IVIg: intravenous immunoglobulin
LDH: lactate dehydrogenase
MG-ADL: Myasthenia Gravis Activities of Daily Living

MGFA: Myasthenia Gravis Foundation of America
PE: plasma exchange
PNH: paroxysmal nocturnal hemoglobinuria

PP: plasmapheresis
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
neostigmine (Bloxxiverz [®])	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),	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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Truxima [®] (rituximab-abbs)* [†]		

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

Indication	Dosing Regimen*	Maximum Dose
PNH, aHUS	IV dosing: Day 1: Loading dose IV Day 15 and thereafter: Maintenance dose IV. If currently receiving SC Ultomiris, administer IV Ultomiris maintenance dose starting 1 week after last SC Ultomiris maintenance dose	IV: 3,600 mg/ 8 weeks SC: 490 mg/week

Indication	Dosing Regimen*			Maximum Dose	
	Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)		
	≥ 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		
	SC dosing (maintenance only for age ≥ 18 years and weight ≥ 40 kg): 490 mg SC per week, starting 2 weeks after IV Ultomiris loading dose or 8 weeks after last IV Ultomiris maintenance dose				
	gMG	Body Weight Range (kg)	Loading Dose (mg)		Maintenance Dose (mg)
≥ 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					
Supple- mental doses	A supplemental dose of Ultomiris is required within 4 hours of PE, PP, or IVIg as they have been shown to reduce Ultomiris serum levels:			See regimen	
	Body Weight Range (kg)	Most Recent Ultomiris Dose (mg)	Supplemental Dose (mg)		
			After PE/PP		After IVIg
	≥ 40 to < 60	2,400	1,200		600
		3,000	1,500		
	≥ 60 to < 100	2,700	1,500		
		3,300	1,800		
	≥ 100	3,000	1,500		
		3,600	1,800		

**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 for IV injection: 300 mg/30 mL, 300 mg/3 mL, 1,100 mg/11 mL
- Single-dose prefilled cartridge for use with supplied single-use on-body injector for SC injection: 245 mg/3.5 mL

VII. References

1. Ultomiris Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc.; July 2022. Available at: www.ultomiris.com. Accessed April 19, 2023.
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 May 8, 2023.
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 May 8, 2023.

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.

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	04/2019	
1Q 2020 annual review: added language to clarify timing of loading dose when switching from Soliris; criteria added for new FDA indication: aHUS; references reviewed and updated.	01/2020	
1Q 2021 annual review: added requirement against concurrent use with Soliris; added new strength vials- 300 mg/3 mL and 1,100 mg/11 mL; references reviewed and updated.	01/2021	
1Q 2022 annual reviewed: RT4: 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.	01/2022	
RT4: criteria added for new FDA indication: gMG.	10/2022	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2023 annual review: no significant changes; RT4: added new SC injection dosage form and updated dosing requirements in criteria and section V (including allowance for supplemental doses if member has received PE, PP, or IVIg); references reviewed and updated.	01/2023	
3Q 2023 annual review: no significant changes; references reviewed and updated.	07/2023	