Clinical Policy Title:	ravulizumab-cwvz
Policy Number:	RxA.289
Drug(s) Applied:	Ultomiris®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of Business

Background

Ravulizumab-cwvz (Ultomiris®) is a complement inhibitor. It is indicated for:

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

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ravulizumab-cwvz (Ultomiris®)	PNH	<u>Recommended Weight-Based (in Kg) Dosage Regimen for PNH:</u> • Body weight 5 to < 10 Loading Dose (mg): 600 mg Maintenance dose: 300 mg every 4 weeks • Body weight 10 to < 20 Loading Dose (mg): 600 mg Maintenance dose: 600 mg every 4 weeks • Body weight 20 to < 30 Loading Dose (mg): 900 mg Maintenance dose: 2100 mg every 8 weeks • Body weight 30 to < 40 Loading Dose (mg): 1200 mg Maintenance dose: 2700 mg every 8 weeks • Body weight 40 to < 60 Loading Dose (mg): 2400 mg Maintenance dose: 3000 mg every 8 weeks • Body weight 60 to < 100 Loading Dose (mg): 2700 mg Maintenance dose: 3300 mg every 8 weeks • Body weight ≥ 100 Loading Dose (mg): 3000 mg Maintenance dose: 3600 mg every 8 weeks For patients switching from eculizumab to Ultomiris®, administer the loading dose of Ultomiris® intravenous 2	3,600 mg/ 8 weeks

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		weeks after the last eculizumab infusion, and then administer maintenance doses intravenous once every 4 weeks or 8 weeks (depending on body weight), starting 2 weeks after loading dose administration.	
ravulizumab-cwvz (Ultomiris®)	aHUS	Recommended Weight-Based (in Kg) Dosage Regimen for aHUS: • Body weight 5 to < 10 Loading Dose (mg): 600 mg Maintenance dose: 300 mg every 4 weeks • Body weight 10 to < 20 Loading Dose (mg): 600 mg Maintenance dose: 600 mg every 4 weeks • Body weight 20 to < 30 Loading Dose (mg): 900 mg Maintenance dose: 2100 mg every 8 weeks • Body weight 30 to < 40 Loading Dose (mg): 1200 mg Maintenance dose: 2700 mg every 8 weeks • Body weight 40 to < 60 Loading Dose (mg): 2400 mg Maintenance dose: 3000 mg every 8 weeks • Body weight 60 to < 100 Loading Dose (mg): 2700 mg Maintenance dose: 3300 mg every 8 weeks • Body weight ≥ 100 Loading Dose (mg): 3000 mg Maintenance dose: 3600 mg every 8 weeks For patients switching from eculizumab to Ultomiris®, administer the loading dose of Ultomiris® intravenous 2 weeks after the last eculizumab infusion, and then administer maintenance doses intravenous once every 4 weeks or 8 weeks (depending on body weight), starting 2 weeks after loading dose administration.	3,600 mg/ 8 weeks

Dosage Forms

- 300 mg/30 mL (10 mg/mL) in a single-dose vial.
- 300 mg/3 mL (100 mg/mL) in a single-dose vial.
- 1,100 mg/11 mL (100 mg/mL) in a single-dose vial.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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 (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. Dose does not exceed (a, b, and c):
   a. If member is switching therapy from Soliris®, administration of the loading dose should occur 2 weeks after the last Soliris® infusion;
   b. Loading dose (Day 1) does not exceed the weight-based loading dose in the Dosing Information;
   c. Maintenance dose (Day 15 and every 4 or 8 weeks thereafter) does not exceed the weight-based maintenance dose in the Dosing Information.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Atypical Hemolytic Uremic Syndrome (must meet all):

1. Diagnosis of aHUS;
2. Prescribed by or in consultation with a nephrologist or hematologist;
3. Age ≥ 1 month;
4. Documentation that patient does not have Shiga toxin E.coli infection;
5. Documentation that patient does not have ADAMTS13 deficiency;
6. Meets all of the following (a, b, and c):
   a. If member is switching therapy from Soliris®, administration of the loading dose should occur 2 weeks after the last Soliris® infusion;
   b. Loading dose (Day 1) does not exceed the weight-based loading dose in the Dosing Information;
   c. Maintenance dose (Day 15 and every 4 or 8 weeks thereafter) does not exceed the weight-based maintenance dose in the Dosing Information.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters:
   a. Improved measures of intravascular hemolysis (e.g., normalization of lactate dehydrogenase [LDH]);
   b. Reduced need for red blood cell transfusions;
   c. Increased or stabilization of hemoglobin levels;
   d. Less fatigue;

e. Improved health-related quality of life;
f. Fewer thrombotic events.

3. If request is for a dose increase, new dose does not exceed the weight-based maintenance dose in the Dosing Information.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Atypical Hemolytic Uremic Syndrome (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy ;
2. Member is responding positively to therapy as evidenced by one of the following parameters (a, b, c, d, or e):
   a. Increase in Platelet count;
   b. decrease in serum creatinine;
   c. decrease in serum LDH;
   d. Reduced need for red blood cell transfusions;
   e. Reduced need for dialysis.
3. If request is for a dose increase, new dose does not exceed the weight-based maintenance dose in the Dosing Information.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
GPI: glycosyl phosphatidylinositol
PNH: paroxysmal nocturnal hemoglobinuria
aHUS: atypical hemolyticuremic syndrome
TMA: thrombotic microangiopathy
STEC-HUS: Shiga toxin E. coli related hemolytic uremic syndrome
ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
LDH: Lactate dehydrogenase

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.

References

1. Ultomiris® Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc.; June 2021 . Available at: www.ultomiris.com. Accessed July 12, 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. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1895106/ . Accessed July 13, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated. 2. Line of Business Policy Applies to was update to all lines of business. 3. Background was updated: Limitations of Use and new Indication (aHUS) were added. 4. Dosing Information: aHUS dosing information was added. 5. PNH approval duration updated to specify Medicaid, HIM and Commercial approval durations. 6. Criteria for aHUS was added. 7. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." in PNH and Continued Therapy criteria was added for aHUS. 8. APPENDIX A was updated to included TMA, aHUS, STEC-HUS. 9. APPENDIX C Boxed Warnings was updated. 10. References were updated.	07/03/2020	09/14/2020
Policy was reviewed: 1. Background was updated from “treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)” to	07/12/2021	09/14/2021

Review/Revision History	Review/Revised Date	P&T Approval Date
"treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH)". 2. Dosing Information dosing regimens for all indications was updated from table format to bullet-list format. 3. Dosing Information dosing regimen for indication PNH was updated to include dosing for lower kg body weights, "Body weight 5 to < 10…", "Body weight 10 to < 20…", "Body weight 20 to < 30…", and "Body weight 30 to < 40…". 4. Dosing Information dosing regimen for indication aHUS was updated from "…administer maintenance doses intravenous once every 8 weeks, starting 2 weeks after loading dose administration" to "…administer maintenance doses intravenous once every 4 weeks or 8 weeks (depending on body weight), starting 2 weeks after loading dose administration.". 5. Dosage Forms was updated from "single-dose vial: 300mg/30mL" to "300 mg/30 mL (10 mg/mL) in a single-dose vial; 300 mg/3 mL (100 mg/mL) in a single-dose vial; 1,100 mg/11 mL (100 mg/mL) in a single-dose vial.". 6. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 7. Initial Approval Criteria I.A.3 age criteria was updated from "Age ≥ 18 years" to "Age ≥ 1 month". 8. Initial Approval Criteria I.A.6.b was updated from listing specific weight-based loading doses (in mg) to "Loading dose (Day 1) does not exceed the weight based loading dose in the Dosing Information;". 9. Initial Approval Criteria I.A.6.c was updated from listing specific weight-based		

Review/Revision History	Review/Revised Date	P&T Approval Date
maintenance doses (in mg) to "Maintenance dose (Day 15 and every 4 or 8 weeks thereafter) does not exceed the weight based maintenance dose in the Dosing Information;". 10. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 11. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 12. Continued Therapy Approval Criteria II.A.3 was updated from listing specific weight-based maintenance doses (in mg) to "If request is for a dose increase, new dose does not exceed the weight-based maintenance dose in the Dosing Information". 13. Continued Therapy Approval Criteria II.B.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 14. Appendix A was updated to include abbreviation LDH. 15. Appendix C Contraindications was updated to include "Patients who are not currently vaccinated against *Neisseria meningitidis*....". 16. References were reviewed and updated.		