Ultomiris® (ravulizumab-cwvz)
(Intravenous)

Document Number: IC-0427

Last Review Date: 10/26/20120
Date of Origin: 02/04/2019
Dates Reviewed: 02/2019, 10/2019, 12/2019, 11/2020

I. Length of Authorization

Coverage will be provided for twelve months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Ultomiris 10 mg/mL – 30 mL SDV: 10 vials on day zero followed by 13 vials starting on day 14 and every 8 weeks thereafter
- Ultomiris 100 mg/mL – 3 mL SDV: 10 vials on day zero followed by 13 vials starting on day 14 and every 8 weeks thereafter
- Ultomiris 100 mg/mL – 11 mL SDV: 3 vials on day zero followed by 3 vials starting on day 14 and every 8 weeks thereafter

B. Max Units (per dose and over time) [HCPCS Unit]:

Indication	Loading Dose Units	Maintenance Dose Units
PNH/aHUS	300 units on Day 0	360 units on Day 14 and every 8 weeks thereafter

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age (unless otherwise specified); **AND**
- Patients must be administered a meningococcal vaccine at least two weeks prior to initiation of therapy and revaccinated according to current medical guidelines for vaccine use *(If urgent Ultomiris therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide patients with two weeks of antibacterial drug prophylaxis.)*; **AND**
- Prescriber is enrolled in the Ultomiris Risk Evaluation and Mitigation Strategy (REMS) program; **AND**

Universal Criteria [1]

- Patient does not have an active systemic infection; **AND**
- Will not be used in combination with other complement-inhibitor therapy (i.e., eculizumab); **AND**

Paroxysmal Nocturnal Hemoglobinuria (PNH) † Φ [1,4,8]

- Used as Soliris switch therapy *(please refer to Section IV for the pertinent renewal criteria)*; **OR**
- Diagnosis must be accompanied by detection of PNH clones of at least 5% by flow cytometry diagnostic testing; **AND**
    - Demonstrate the presence of at least 2 different glycosylphosphatidylinositol (GPI) protein deficiencies (e.g., CD55, CD59, etc.) within at least 2 different cell lines (granulocytes, monocytes, erythrocytes); **AND**
- Patient has one of the following indications for therapy:
    - Presence of a thrombotic event
    - Presence of organ damage secondary to chronic hemolysis
    - Patient is pregnant and potential benefit outweighs potential fetal risk
    - Patient is transfusion dependent
    - Patient has high LDH activity (defined as ≥1.5 x ULN) with clinical symptoms
- Documented baseline values for one or more of the following (necessary for renewal): serum lactate dehydrogenase (LDH), hemoglobin level, and packed RBC transfusion requirement

Atypical Hemolytic Uremic Syndrome (aHUS) † [1,5,7]

- Used as Soliris switch therapy *(please refer to Section IV for the pertinent renewal criteria)*; **OR**
- Patient is at least 1 month of age; **AND**
- Patient shows signs of thrombotic microangiopathy (TMA) (e.g., changes in mental status, seizures, angina, dyspnea, thrombosis, increasing blood pressure, decreased platelet count, increased serum creatinine, increased LDH, etc.); **AND**
- Thrombotic Thrombocytopenic Purpura (TTP) has been ruled out by evaluating ADAMTS-13 level (ADAMTS-13 activity level > 10%); **AND**
- Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS) has been ruled out; **AND**
- Other causes have been ruled out such as coexisting diseases or conditions (e.g., bone marrow transplantation, solid organ transplantation, malignancy, autoimmune disorder, drug-induced, etc.) or known genetic defect in cobalamin C metabolism; **AND**
- Documented baseline values for one or more of the following (necessary for renewal): serum lactate dehydrogenase (LDH), serum creatinine/eGFR, platelet count, and dialysis requirement

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1]

Coverage may be renewed based upon the following criteria:

- Used as switch therapy, for a diagnosis of PNH or aHUS, if a patient has shown a beneficial disease response and absence of unacceptable toxicity while on Soliris; **OR**
- Patient continues to meet the universal and other indication-specific relevant criteria identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: serious meningococcal infections (septicemia and/or meningitis), infusion reactions, other serious infections (i.e. *Streptococcus pneumoniae, Haemophilus influenzae*, *Neisseria gonorrhoeae)*, thrombotic microangiopathy (TMA) complications, etc.; **AND**
- Disease response indicated by one or more of the following:
  - PNH [1,4,8]
    - Decrease in serum LDH from pretreatment baseline
    - Stabilization/improvement in hemoglobin level from pretreatment baseline
    - Decrease in packed RBC transfusion requirement from pretreatment baseline
  - aHUS [1,5,7]
    - Decrease in serum LDH from pretreatment baseline
    - Stabilization/improvement in serum creatinine/eGFR from pretreatment baseline
    - Increase in platelet count from pretreatment baseline
    - Patient no longer requires dialysis treatments

V. Dosage/Administration

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td>Paroxysmal nocturnal hemoglobinuria (PNH)</td><td><u>Complement-Inhibitor Therapy Naïve*</u>
Administer the loading dose based on weight. Two weeks later, begin maintenance doses at a once every 8-week interval:
<table>
<tr><th>Body Weight Range</th><th>Loading Dose (mg)</th><th>Maintenance Dose (mg)</th></tr>
<tr><td>≥40 kg - <60 kg</td><td>2,400</td><td>3,000</td></tr>
<tr><td>≥60 kg - <100 kg</td><td>2,700</td><td>3,300</td></tr>
<tr><td>≥100 kg</td><td>3,000</td><td>3,600</td></tr>
</table>
*Note: for Soliris switch therapy please refer to the package insert for appropriate switch dosing.</td></tr>
<tr><td>Atypical Hemolytic Uremic Syndrome (aHUS)</td><td><u>Complement-Inhibitor Therapy Naïve*</u>
Administer the doses based on the patient's body weight. Starting 2 weeks after the loading dose, begin maintenance doses once every 8 weeks or every 4 weeks (depending on body weight)
<table>
<tr><th>Body Weight Range</th><th>Loading Dose (mg)</th><th>Maintenance Dose (mg)</th><th>Dosing Interval</th></tr>
</table></td></tr>
</table>

≥5 kg - <10 kg	600	300	Every 4 weeks
≥10 kg - <20 kg	600	600	Every 4 weeks
≥20 kg - <30	900	2,100	Every 8 weeks
≥30 kg - <40 kg	1,200	2,700	Every 8 weeks
≥40 kg - <60 kg	2,400	3,000	Every 8 weeks
≥60 kg - <100 kg	2,700	3,300	Every 8 weeks
≥100 kg	3,000	3,600	Every 8 weeks

**Note: for Soliris switch therapy please refer to the package insert for appropriate switch dosing.*

VI. Billing Code/Availability Information

HCPCS Code:

- J1303 – Injection, ravulizumab-cwvz, 10 mg; 1 billable unit = 10 mg

NDC:

- Ultomiris 300 mg/3 mL single-use vials for injection: 25682-0025-xx
- Ultomiris 300 mg/30 mL single-use vials for injection: 25682-0022-xx
- Ultomiris 1100 mg/11 mL single-use vials for injection: 25682-0028-xx

VII. References

1. Ultomiris [package insert]. Boston, MA; Alexion Pharmaceuticals, Inc; October 2020. Accessed October 2020.
2. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Borowitz MJ, Craig FE, DiGiuseppe JA, Illingworth AJ, Rosse W, Sutherland DR, Wittwer CT, Richards SJ. Cytometry B Clin Cytom. 2010 Jul;78(4):211-30. doi: 10.1002/cyto.b.20525.
3. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005 Dec 1. 106(12):3699-709.
4. Sahin F, Akay OM, Ayer M, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016;6(2): 19-27.
5. 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 Jan;31(1):15-39.
6. Taylor CM, Machin S, Wigmore SJ, et al. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol. 2010 Jan;148(1):37-47.
7. Cheong HI, Kyung Jo S, Yoon SS, et al. Clinical Practice Guidelines for the Management of Atypical Hemolytic Uremic Syndrome in Korea. J Korean Med Sci. 2016 Oct;31(10):1516-1528.
8. Brodsky RA, Peffault de Latour R, Rottinghaus ST, Röth A, Risitano AM, Weitz IC, Hillmen P, Maciejewski JP, Szer J, Lee JW, Kulasekararaj AG, Volles L, Damokosh AI, Ortiz S, Shafner L, Liu P, Hill A, Schrezenmeier H. Characterization of breakthrough

hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Haematologica. 2020 Jan 16. pii: haematol.2019.236877. doi: 10.3324/haematol.2019.236877. [Epub ahead of print]

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D59.3	Hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Articles (LCAs) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCA/LCD): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC