Drug Monograph

Drug/Drug Class:	**Ultomiris™ (ravulizumab-cwvz) for injection / Monoclonal Antibody, Complement Inhibitor**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Ultomiris™ is available as a 300 mg/30 mL (10 mg/mL) single-dose vial. Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard, Boston, MA 02210.
Summary of Findings:	In two open-label, non-inferiority, randomized, active-controlled phase 3 trials (N=441) showed statistically improvement in primary outcomes for treatment naïve patients and demonstrated non-inferiority compared to Soliris® throughout both studies. During the 183 Day trials the most common adverse reactions with Ultomiris™ were upper respiratory tract infections and headache. Patients should be monitored for signs and symptoms of illness as this can become life-threatening in addition to thromboembolic events, infusion reactions and disease manifestations after therapy discontinuation.

Status Recommendation:	☒ Prior Authorization (PA) Required	☐ Open Access
	☐ Clinical Edit	☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE	☐ Non-Preferred Agent
	☒ Appropriate Indications and Trial	☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare and chronic disease originating from a defect in the complement system that leads to the destruction of red blood cells (RBCs). This breakdown of RBCs leads to an increase in hemoglobin in the urine which produces a dark-colored urine in the morning. PNH typically presents in early adulthood and diagnosis of the disease is difficult because of the variety of symptoms. PNH is unique in that it is accompanied with hemolytic anemia, thrombosis and pancytopenia and can present as primary, develops on its own, or secondary, develops in context with other bone marrow disorders. Defective or lacking surface proteins on RBCs, particularly decay-accelerating factor (DAF), fail to regulate the complement-regulating system leading to attacks of the RBCs in the blood vessels causing hemolysis. Bone marrow transplant is the only true curative treatment for PNH however this can be difficult with potential for additional medical problems. For patients that are asymptomatic, or patients with mild symptoms, symptomatic therapy may be considered. For symptomatic patients, the main treatment option is to interrupt the complement system. To date there are two complement inhibitors available, Soliris® introduced in 2007 and Ultomiris™ introduced in 2018. These medications are not curative therefore must be continued indefinitely or patients risk symptom return.

Dosage Form(s) [1]

Ultomiris™ is available as a 300 mg/30 mL (10 mg/mL) single-dose vial.

Manufacturer [1]

Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard, Boston, MA 02210.

Indication(s) [1]

Ultomiris™ is indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in adult patients.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Ultomiris™ is a humanized monoclonal antibody that binds to the complement protein C5 and inhibiting the breakdown to C5a and C5b. This system ultimately prevents the formation of C5b9 which when activated leads to cell lysis. Ultomiris™ is approved for treatment of adult patients with paroxysmal nocturnal hemoglobinuria.

Pharmacokinetics:

	Ultomiris™
Volume of Distribution	5.34 L

Excretion	Clearance 0.08 Liter per day
Half-life	49.7 Days

Efficacy in Treatment of PNH

STUDY DESIGN	Two open-label, non-inferiority, randomized, active-controlled phase 3 trials. The two trials were named PNH Study 301 (N=246) and PNH 302 (N=195). Study 301 studied efficacy as defined by transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Study 302 studied efficacy as defined by hemolysis as measured by LDH percentage change from baseline to Day 183.
INCLUSION CRITERIA	Study 301 included adult patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 included adult patients with PNH who were clinically stable after having been treated with Soliris® for at least the past 6 months.
EXCLUSION CRITERIA	The study excluded patients that did not meet the inclusion criteria.
TREATMENT REGIMEN	Patients in both studies were randomized to receive Ultomiris™ or Soliris®. Patients randomized to Ultomiris™ received a loading dose followed by maintenance dosing every 8 weeks as defined by manufacturer weight-based dosage guidelines. The Soliris® group had a dose administered on Days 1, 8, 15 and 22 followed by maintenance treatment with 900 mg on Day 29 and every 2 weeks thereafter. In both studies, patients were either vaccinated against meningococcal infection prior to treatment or received prophylactic antibiotics for a minimum of 2 weeks prior to starting therapy.
RESULTS	Study 301 patients had a transfusion avoidance (did not receive a transfusion and did not meet the protocol guidelines for transfusion from baseline) of 73.6% for the Ultomiris™ group and 66.1% in the Soliris® group (CI 95%). Ultomiris™ also showed a 53.6% LDH normalization compared to 49.4% for Soliris® (CI 95%). Study 302 showed LDH percent change of -0.82% for Ultomiris™ and 8.4% for Soliris® (CI 95%). Supportive efficacy for each study included breakthrough hemolysis and proportion of patients with stabilized hemoglobin. Non-inferiority for Ultomiris™ was demonstrated across all endpoints in both studies.
SAFETY	The most common adverse reactions were upper respiratory tract infection and headache. A serious adverse reaction was reported in 15 patients, hyperthermia and pyrexia, and one fatal case of sepsis was identified in a patient with the Ultomiris™ group. It should be noted, due

	to Ultomiris™ blocking terminal complement activation, patients may be more susceptible to bacterial infections.

Contraindications (1)

- Ultomiris™ is contraindicated in patients with unresolved *Neisseria meningitidis* infection.

Warnings and Precautions (1)

Ultomiris™ has several warnings and precautions associated with its use:

- Serious Meningococcal Infections: Treatment with Ultomiris™ increases patient susceptibility of serious and life-threatening meningococcal infection. This has led to Ultomiris™ requiring a Risk Evaluation and Mitigation Survey (REMS) program for prescribers and patient education including meningococcal vaccination.
- Other Infections: Patients should be monitored for sign and symptoms of infection.
- Monitoring Disease Manifestations after Ultomiris™ Discontinuation: Patients should be monitored for signs and symptoms hemolysis for at least 16 weeks after discontinuing therapy.
- Thromboembolic Event Management: Treatment with Ultomiris™ along with anticoagulation has not been established.
- Infusion Reactions: Monitor patients for infusions reactions while using Ultomiris™ and institute appropriate supportive measures.

Adverse Effects (1)

Most common, ≥ 5%	**Ultomiris™**	**Soliris®**
Diarrhea	9%	5%
Nausea	9%	9%
Abdominal Pain	6%	7%
Pyrexia	7%	8%
Upper Respiratory Tract Infection	39%	39%
Pain in Extremity	6%	5%
Arthralgia	5%	5%
Headache	32%	26%
Dizziness	5%	6%

Drug Interactions (1)

- While there are no direct interactions according to the drug literature, as with any

immunosuppressant, interactions are possible.

Dosage and Administration [1]

Ultomiris™ is an intravenous infusion with both a loading dose and maintenance dosing:

- The loading dose is between 2400 and 3000 mg based on weight.
- Starting at week 2 after loading dose, the maintenance dose is given once every 8 weeks. This is also based on weight between 3000 and 3600 mg per dose.

Ultomiris™ is to be administered at a diluted concentration of 5 mg/mL in 0.9% Sodium Chloride Injection using aseptic technique. Healthcare providers must enroll in the Ultomiris REMS and in addition to patients being vaccinated for meningococcal disease according to current ACIP guidelines. Patients that need to start Ultomiris™ immediately, or less than 2 weeks after vaccination, should be given 2 weeks of antibacterial prophylaxis before starting Ultomiris™ therapy.

Cost

BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/VIAL
Ultomiris™	Alexion	300 mg/30 mL	2400-3000 mg Loading Dose then 3000-3600 Maintenance Dose in 2 Weeks & Every 8 Weeks Thereafter***	$6,404*
Soliris®	Alexion	300 mg/30 mL	600 mg Weekly x4 Weeks, 900 mg at Week 5 then 900 mg Every 2 Weeks	$6,496.80**

** Wholesale Acquisition Cost*
***Maximum Allowable Cost*
****Weight Based Dosing Regimen*

Conclusion

Ultomiris™ is a humanized monoclonal antibody that binds to the complement protein C5 and inhibiting the breakdown to C5a and C5b. In two open-label, non-inferiority, randomized, active-controlled phase 3 trials (N=441) showed statistically improvement in primary outcomes for treatment naïve patients and demonstrated non-inferiority compared to Soliris® throughout both studies. The most common adverse reactions were upper respiratory tract infection and headache and it should be noted that patients taking Ultomiris™ are at a higher risk of encapsulated bacterial infections. To date, there are just two medications that are complement inhibitors. Ultomiris™ has an advantage in dosing convenience in that it is recommended to be given once every 8 weeks for maintenance therapy versus every 2 weeks with Soliris®. Patients should be vaccinated against meningococcal disease, or treated with prophylactic antibiotics for at least 2 weeks, before starting Ultomiris™. Providers must also enroll in the Ultomiris REMS program before starting patients on therapy. Patients should be monitored for signs and symptoms of illness as this can become life-

threatening in addition to thromboembolic events, infusion reactions and disease manifestations after therapy discontinuation.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Product Information: Ultomiris™ (ravulizumab-cwz), Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard, Boston MA 02210 12/2018.
2) Besa, Emmanuel MD, Krishnan, Koyamangalath MD et al. Paroxysmal Nocturnal Hemoglobinuria January 02,2019 Medscape.

Prepared by: Tyler Woods PharmD
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