New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	Ultomiris® (ravulizumab-cwvz) [Alexion Pharmaceuticals]
Dosage Formulations:	300mg / 30ml single dose vial
FDA Approval Date: **FDB File Date:**	FDA: December 21, 2018 FDB: December 30, 2018
Indication:	Treatment of paroxysmal nocturnal hemoglobinuria (PNH) in adults
Mechanism of Action:	Ultomiris® is a terminal complement inhibitor that specifically binds to the complement protein C5 inhibiting its cleavage to C5a and C5b and preventing generation of the terminal complement complex C5b9. Ultomiris™ inhibits terminal complement-medicated intravascular hemolysis in patients with PNH.
Dose/ Administration:	IV infusion that is based on weight at time of treatment: ≥40kg to <60kg: • Loading dose: 2,400mg • Maintenance dose: 3,000mg once every 8 weeks starting 2 weeks after the loading dose ≥60kg to <100kg: • Loading dose: 2,700mg • Maintenance dose: 3,300mg once every 8 weeks starting 2 weeks after the loading dose ≥100kg: • Loading dose: 3,00mg • Maintenance dose: 3,600mg once every 8 weeks starting 2 weeks after the loading dose Vaccinate with meningococcal vaccine at least 2 weeks prior to treatment initiation
Drug Clinical Highlights:	BBW and REMS Program: Life-threatening meningococcal infections and/or sepsis have occurred in patients treated with Ultromiris and may become rapidly life-threatening or fatal if not recognized and treated early. REMS requirements: Provider must enroll in the program and counsel patients on the risks of meningococcal infection, provide the patient with the REMS educational materials and ensure patients are vaccinated with meningococcal vaccines. Estimated incidence of PNH is in the range of 1-10 cases per million. Contraindications: patients with unresolved *Neisseria Meningitidis* infection ALXN1210-PHN-301 and ALXN1210-PHN-302: Two open-label, randomized, active-controlled, non-inferiority Phase 3 studies. PNH Study 301 enrolled 246 complement inhibitor naïve patients who had active hemolysis. PNH Study 302 enrolled 195 patients who were clinically stable after having been treated with Soliris® for at least the past 6 months. In the PNH Study 301 patients were randomized 1:1 to either Ultomiris™ or Soliris®. The study established efficacy based upon transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the

presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy and the proportion of patients with stabilized hemoglobin.

Table 7: Efficacy Results in the Complement-Inhibitor Naïve Study

	ULTOMIRIS (N=125)	Eculizumab (N=121)	Statistic for Comparison	Treatment Effect (95% CI)
Transfusion avoidance rate	73.6%	66.1%	Difference in rate	6.8 (-4.66, 18.14)
LDH normalization	53.6%	49.4%	Odds ratio	1.19 (0.80, 1.77)
LDH percent change	-76.84%	-76.02%	Difference in % change from baseline	-0.83 (-5.21, 3.56)
Breakthrough hemolysis	4.0%	10.7%	Difference in rate	-6.7 (-14.21, 0.18)
Hemoglobin stabilization	68.0%	64.5%	Difference in rate	2.9 (-8.80, 14.64)

Note: LDH = lactate dehydrogenase; CI = confidence interval

In the PNH Study 302 patient were randomized 1:1 to either Ultomiris™ or Soliris®. The study established efficacy based on hemolysis as measured by LDH percent change from baseline to Day 183 and supportive efficacy data was transfusion avoidance, proportion of patients with stabilized hemoglobin and the proportion of patients with breakthrough hemolysis through Day 183.

Table 9: Efficacy Results in the Eculizumab-Experienced Patients with PNH Eculizumab-Experienced Study

	ULTOMIRIS n = 97	Eculizumab n = 98	Statistic for Comparison	Treatment Effect (95% CI)
LDH Percent change	-0.82%	8.4%	Difference in % change from baseline	9.2 (-0.42, 18.8)
Breakthrough hemolysis	0%	5.1%	Difference in rate	5.1 (-8.9, 19.0)
Transfusion avoidance	87.6%	82.7%	Difference in rate	5.5 (-4.3, 15.7)
Hemoglobin Stabilization	76.3%	75.5%	Difference in rate	1.4 (-10.4, 13.3)

Note: CI = confidence interval

Non-inferiority of Ultomiris™ to Soliris® was demonstrated across endpoints in both studies.

The highest reported adverse reactions in both studies included upper respiratory infection and headaches.

Price Per Unit (WAC): $6,404 per 30ml vial (WAC)

Therapeutic Alternatives:

Only cure is allogenic bone marrow transplant

Drug	Dosing
Ultomiris®	Every 8 weeks (after loading dose)
Soliris®	Twice weekly

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Appropriate diagnosis of PNH (ICD 10 Code: D59.5)
- ≥18 years of age
- Prescribed by or in consultation with a hematologist, oncologist or immunology specialist
- LDH level of 1.5 times the upper limit of the normal range
- Absence of a Soliris® claim in the past two weeks

Initial approval for 6 months

Continuation of Therapy:

- Improvement in fatigue and quality of life
- Documentation demonstrating a positive clinical response from baseline:
  - Increased or stabilization of hemoglobin levels
  - Reduction in transfusions

Optional Provider Monitoring Criteria, if desired:

- Patient received meningococcal vaccine at least two weeks before initiation
- Symptoms of thromboembolic complications (abdominal pain, shortness of breath, chest pain, end organ damage)
- Laboratory confirmed diagnosis of PNH as evidenced by having detectable GPI-deficient hematopoietic clones (Type III PNH RBC) via flow cytometry
  - Flow cytometry testing must include at least 2 different reagents testes on at least 2 cell lineages
- Documentation of greater than 50% of GPI-AP-deficient polymorphonuclear cells and one of the following:
  - Patient is transfusion dependent as defined as one of the following:
    - Hemoglobin ≤ 7 g/dL
    - Both of the following:
      - Hemoglobin ≤ 9 g/dL

Patient is experiencing symptoms of anemia

References:

- Ultomiris® (ravulizumab-cwvz) [prescribing information]. Boston, MA: Alexion Pharmaceuticals; June 2021.
- IPD Analytics: New Drug Review: Ultomiris® (ravulizumab). December 2018
- Ravulizumab-cwvz. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at http://online.lexi.com