Widen the world for your patients with PNH

Jonathan[a]: a 35-year old male, naïve to complement inhibition, complains of erectile dysfunction, fatigue and dyspnea. When you diagnosed him with PNH 5 years ago, he was reluctant to start treatment with eculizumab due to the need for frequent infusions and his busy work schedule. Jonathan is currently managed by his PCP with supportive care measures, but he is considering a new alternative since his symptoms have worsened and are causing limitations at work.

[a]The narrative was adapted from an actual patient case from the ULTOMIRIS naïve (301) clinical trial.[1]

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

Please see accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis. Please see additional Important Safety Information on inside flap.

US/ULT-P/0025 09/22

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

INDICATION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

Subcutaneous Use in Adult Patients with PNH
Subcutaneous administration of ULTOMIRIS is not approved for use in pediatric patients.

SELECT IMPORTANT SAFETY INFORMATION

WARNING:
SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection. See *Warnings and Precautions* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS REMS.

CONTRAINDICATIONS

- 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.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections
Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Meningococcal disease due to any serogroup may occur.

Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies. Immunize patients without history of meningococcal vaccination at least 2 weeks prior to the first dose of ULTOMIRIS. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving meningococcal vaccine(s) must receive appropriate prophylactic antibiotics until 2 weeks after vaccination.

In clinical studies, 59 adult patients with PNH were treated with ULTOMIRIS less than 2 weeks after meningococcal vaccination. All of these patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. In clinical studies with ULTOMIRIS, <1% of patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS. All were adult patients with PNH who had been vaccinated. These patients recovered while continuing treatment with ULTOMIRIS. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

ULTOMIRIS REMS
Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under a REMS called ULTOMIRIS REMS.

Under the ULTOMIRIS REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

Additional information on the REMS requirements is available at www.ultomirisrems.com or 1-888-765-4747.

Other Infections
Patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Children treated with ULTOMIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP guidelines. If ULTOMIRIS is administered to patients with active systemic infections, monitor closely for worsening infection.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

SELECT IMPORTANT SAFETY INFORMATION (cont'd)

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation
After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

Thromboembolic Event Management
The effect of withdrawal of anticoagulant therapy during treatment with ULTOMIRIS has not been established. Treatment should not alter anticoagulant management.

Infusion-Related Reactions
Intravenous or subcutaneous administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

Injection Site Reactions- Subcutaneous administration
27% (23/84) of patients treated with subcutaneous administration of ULTOMIRIS experienced injection site reactions which included application site rash, device allergy, infusion site pain, infusion site reaction, injection site bruising, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, medical device site bruise, medical device site erythema, medical device site hematoma, medical device site induration, medical device site pruritus, medical device site rash, and medical device site reaction.

Allergies to Acrylic Adhesives
The on-body injector of ULTOMIRIS uses acrylic adhesive. For patients with a known allergy to acrylic adhesive, use of this product may result in an allergic reaction. Premedication can be considered, and supportive measures should be instituted if signs of allergy appear.

ADVERSE REACTIONS
Adverse reactions reported in 5% or more of patients treated with ULTOMIRIS vs. Eculizumab was Upper respiratory tract infection (39% vs. 39%), Headache (32% vs. 26%), Diarrhea (9% vs. 5%), Nausea (9% vs. 9%), Pyrexia (7% vs. 8%), Pain in extremity (6% vs. 5%), Abdominal pain (6% vs. 7%), Dizziness (5% vs. 6%), Arthralgia (5% vs. 5%). Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS. One fatal case of sepsis was identified in a patient treated with ULTOMIRIS. In clinical studies, clinically relevant adverse reactions in 1% of adult patients include infusion-related reactions.

Adverse reactions reported in 10% or more of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced was Anemia (20% vs. 25%), Abdominal pain (0% vs. 38%), Constipation (0% vs. 25%), Pyrexia (20% vs. 13%), Upper respiratory tract infection (20% vs. 75%), Pain in extremity (0% vs. 25%), Headache (20% vs. 25%).

Adverse Reactions for Subcutaneous Administration of ULTOMIRIS
Most common adverse reactions (≥10%) with ULTOMIRIS subcutaneous administration via On Body Injector in adult patients with PNH were local injection site reactions, diarrhea, and headache.

DRUG INTERACTIONS
Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins
Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS.

Neonatal Fc Receptor Blockers
Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers (e.g., efgartigimod) may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS.

Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ALEXION
AstraZeneca Rare Disease

US/ULT-P/0025 09/22

Jonathan's Diagnostic Journey

2011

Patient History
Age: 30

Clinical Presentation
Erectile dysfunction, thrombocytopenia, and modest anemia

Lab Values
Hb, g/dL: 10
PLT, x 10^9/L: 90
WBC x 10^9/L: 3.6
LDH, U/L: 650
Coombs Test: Negative

Diagnosis
Owing to the presence of Coombs-negative hemolytic anemia, HSFC was performed on peripheral blood to evaluate for PNH, and a 34% granulocyte clone size was identified

Management
Against medical advice, the patient declined treatment with eculizumab for personal reasons at this time. He was started on supportive care with iron, B-12, and folic acid supplementation, and was subsequently lost to follow up when he moved away for work

Late 2016

Current Visit
December
Age: 35

Clinical Presentation
Recurrent erectile dysfunction, fatigue, and dyspnea on exertion

Lab Values
Hb, g/dL: 9.6
PLT, x 10^9/L: 87
WBC x 10^9/L: 2.7
LDH, U/L: 1552

PNH Monitoring
HSFC was performed on peripheral blood to monitor the PNH granulocyte clone size, which had increased from 34% to 56% in 5 years

Management
Jonathan was still concerned about a frequent infusion schedule. However, since he was **naïve to complement inhibition**, he was considered for inclusion in the 301 study. After counseling and meningococcal vaccination, he was randomized to receive ULTOMIRIS infusions Q8W[a]

2017

May
(Study 301 Entry Point)
Age: 36

Study Entry Pre-screen Clinical Presentation
Persistent erectile dysfunction, fatigue and dyspnea have worsened

Pre-screen Lab Values
Hb, g/dL: 7.1
PLT, x 10^9/L: 80
WBC x 10^9/L: 2.7
LDH, U/L: 1783

PNH Monitoring
Granulocyte clone: 63%
Monocyte clone: 77.9%
Erythrocyte clone: 56.0%

FACIT-Fatigue[b] Score
29.7

Management
Started on ULTOMIRIS; patient was transfusion independent

August
(Study 301-3 Month Follow-Up[d])
Age: 36

Clinical Presentation
Dyspnea and fatigue improved and erectile dysfunction resolved

Lab Values
Hb, g/dL: 12.3
PLT, x 10^9/L: 89
WBC x 10^9/L: 3.1
LDH, U/L: 258

FACIT-Fatigue Score
34.3

Adverse Events
Patient experienced headache after the first and second ULTOMIRIS infusions

Management
ULTOMIRIS

November
(Study 301-6 Month Follow-Up)
Age: 36

Clinical Presentation
Fatigue continued to improve, daily activities and work schedule have normalized

Lab Values
Hb, g/dL: 11.0
PLT, x 10^9/L: 70
WBC x 10^9/L: 3.2
LDH, U/L: 232

PNH Monitoring
Granulocyte clone: 74.6%
Monocyte clone: 80.1%
Erythrocyte clone: 73.0%

FACIT-Fatigue Score
35.7

Adverse Events
Patient experienced upper respiratory tract infection during week 22

Management
ULTOMIRIS

2018

May
(Study 301-12 Month Follow-Up[e])
Age: 37

Clinical Presentation
Reduction of hemolysis and improvements of clinical parameters observed and sustained within 1 year of ULTOMIRIS treatment

Pre-screen Lab Values
Hb, g/dL: 11.7
PLT, x 10^9/L: 74
WBC x 10^9/L: 3.2
LDH, U/L: 193

PNH Monitoring
Granulocyte clone: 79.8%
Monocyte clone: 83.5%
Erythrocyte clone: 80.0%

FACIT-Fatigue Score
36.5

Adverse Events
No additional adverse events reported

Management
ULTOMIRIS; patient remained transfusion independent

Individual results may vary

Prior to entering Study 301, the patient was reluctant to start treatment with eculizumab Q2W due to his busy work schedule and the need for frequent infusions.

The long terminal elimination half-life of ULTOMIRIS allows patients to receive infusions at eight-week dosing intervals.[2,a,c]

Reference Ranges[f]: **Hb, g/dL:** 13.2-17.1 **PLT, x 10^9/L:** 140-400 **WBC x 10^9/L:** 3.8-10.8 **LDH, U/L:** 246 ULN

FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; HSFC, high-sensitivity flow cytometry; LDH, lactate dehydrogenase; PLT, platelets; PNH, paroxysmal nocturnal hemoglobinuria; Q2W, every 2 weeks; Q8W, every 8 weeks; ULN, upper limit of normal; WBC, white blood cells.
[a]Starting 2 weeks after the initial loading dose, maintenance doses are administered once every 8 weeks.[2] [b]FACIT-Fatigue scores ranges from 0-52, with lower scores indicating more severe fatigue.[3] FACIT-Fatigue is self-reported, and patients were not blinded to treatment assignment. [c]The mean (%CV) terminal elimination half-life and clearance of ULTOMIRIS in patients with PNH are 49.7 (18.0) days and 0.08 (29.5) L/day, respectively.[2] [d]Lab values were taken routinely throughout the trial. Efficacy endpoints were evaluated at 26 weeks. [e]Based on physician follow up with patient.[1] The randomized clinical trial concluded at 26 weeks. Individual results may vary. [f]Reference ranges for Hb, PLT WBC from Quest Diagnostics; reference range for LDH from study 301.

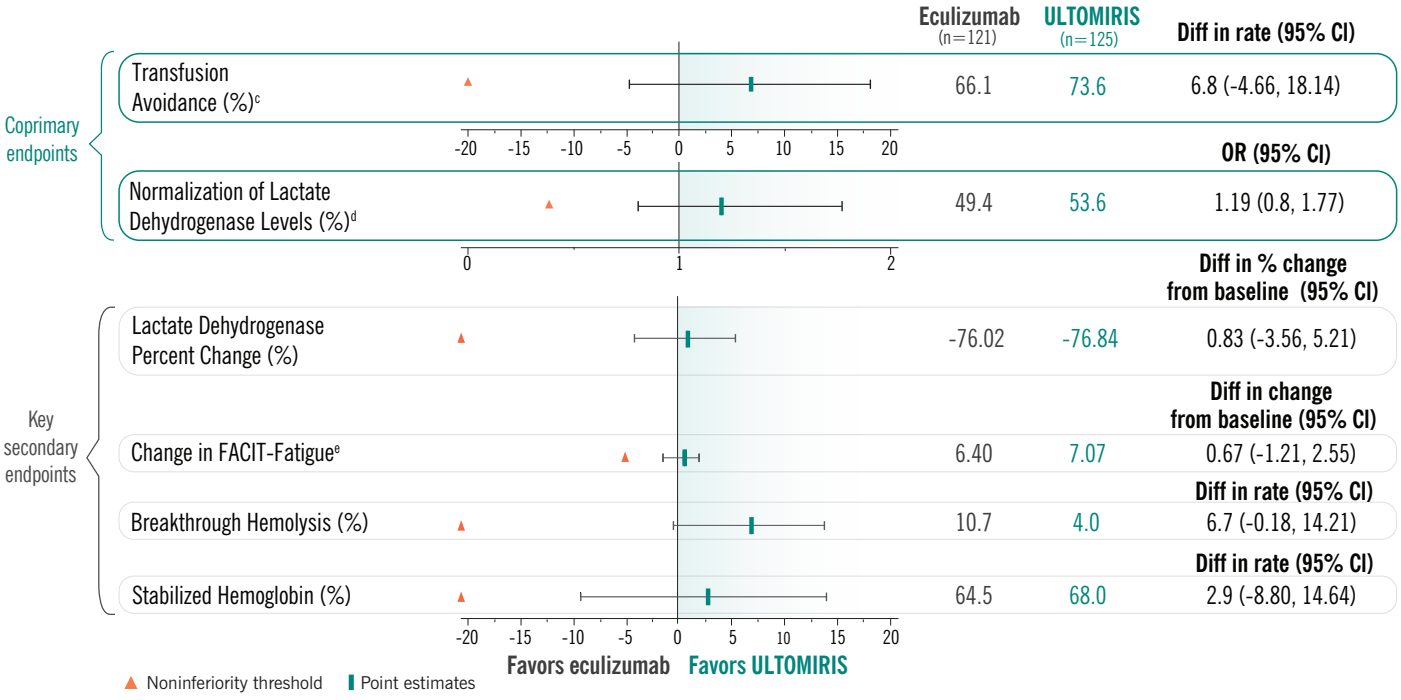
US/ULT-P/0025 09/22

CONSIDER ULTOMIRIS FOR YOUR PATIENTS WITH PNH

The first and only long-acting complement inhibitor that provides immediate and complete C5 inhibition for 8 weeks[2,a]

The 301 study was a 26-week, multicenter, open-label, randomized, active-controlled, noninferiority phase 3 study conducted in 246 patients naive to complement inhibitor treatment prior to study entry. It consisted of a 4-week screening period and a 26-week randomized treatment period to evaluate the efficacy and safety of ULTOMIRIS versus eculizumab, followed by an extension period of up to 2 years during which all patients received ULTOMIRIS.[4]

STUDY 301 EFFICACY RESULTS ACROSS COPRIMARY[b] AND KEY SECONDARY ENDPOINTS[4,b]



- **ULTOMIRIS demonstrated noninferior efficacy across all endpoints vs eculizumab[4]**
- **ULTOMIRIS, built on the foundation of eculizumab, has a ~4x longer half-life[2,5,f]**
- **The safety profile of ULTOMIRIS in patients with PNH who were naïve to complement inhibitor therapy was comparable to that of eculizumab; no discontinuations due to treatment-related AEs occurred in the ULTOMIRIS treatment group[4]**
- **The 4 most common AEs occurring in ≥5% of patients in the ULTOMIRIS and eculizumab groups were headache (36% vs 33.1%), nasopharyngitis (8.8% vs 14.9%), nausea (8.8% vs 8.3%), and upper respiratory tract infection (10.4% vs 5.8%)[4]**
- **Eleven patients in the ULTOMIRIS group and 9 patients in the eculizumab group experienced serious adverse events[g]**

AE, adverse event; Diff, difference; FACIT, Functional Assessment of Chronic Illness Therapy; OR, odds ratio.

[a]Starting 2 weeks after the initial loading dose, maintenance doses are administered once every 8 weeks.[2] [b]Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol-specified guidelines for transfusion from baseline to Day 183. Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2x ULN, after prior LDH reduction to <1.5x ULN on therapy.[4] [c]For the transfusion avoidance end point, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI. [d]For the LDH normalization end point, the adjusted prevalence within each treatment is displayed. [e]There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared with baseline, as measured by the FACIT-Fatigue instrument. Patient-reported fatigue may be an under- or overestimation, because patients were not blinded to treatment assignment.[2] [f]The mean (%CV) terminal elimination half-life and clearance of ULTOMIRIS in patients with PNH are 49.7 (18.0) days and 0.08 (29.5) L/day, respectively.[2] Half-life of eculizumab is 11.25 to 17.25 days.[5] [g]Serious adverse events in the ULTOMIRIS group included: anemia, aplastic anemia, neutropenia, thrombocytopenia, left ventricular failure, myocardial ischemia, pyrexia, leptospirosis, systemic infection, laceration, uterine leiomyoma, renal colic, and deep vein thrombosis (n=1 patient each). Serious adverse events in the eculizumab group included: pyrexia (n=2 patients), ileus, neutropenic colitis, limb abscess, cellulitis, infection, pneumonia, viral upper respiratory tract infection, adenocarcinoma of colon, lung adenocarcinoma, and paroxysmal nocturnal hemoglobinuria (n=1 patient each). Serious infections in this study resolved without sequelae.

1. Data on file. Alexion Pharmaceuticals, Inc.; 2019. **2.** ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **3.** Cella D, et al. *J Pain Symptom Manage*. 2002;24(6):547-561. **4.** Lee JW, et al. *Blood*. 2019;133(6):530-539. **5.** SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.

Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial