Alexion: A Long-Standing History of Commitment to Supporting Patients with Rare Diseases

1992 — Alexion founded

2007 — Eculizumab first approved

2008 — Prix Galien USA Best Biotechnology Product —Eculizumab

2009 — Prix Galien France Drugs for Rare Diseases —Eculizumab

2011 — Eculizumab approved for additional indications

2018 — ULTOMIRIS approved for adults with PNH

2019 — ULTOMIRIS approved for atypical-HUS[a]

2019 — Prix Galien USA Nominated: Best Biotechnology Product —ULTOMIRIS

With **20 years of complement research** experience and over a decade of providing complement inhibition in the clinical setting, **Alexion** is committed to bringing therapies to patients with rare diseases.

ULTOMIRIS, **built on the foundation of eculizumab**, has an ~4x longer half life[b,c]

ULTOMIRIS provides **immediate, complete, and sustained** inhibition of C5 for up to 8 weeks[d]

ULTOMIRIS is now the **number one prescribed complement inhibitor** for PNH and preferred by patients with PNH[4,5,e]

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INDICATIONS

4
PHASE 3 CLINICAL TRIALS

>500
PATIENTS STUDIED

ONESOURCE®
Personalized Patient Support from Alexion

1.888.765.4747
OneSource@Alexion.com

Alexion's support programs connect patients, families, and caregivers facing complement-mediated diseases with a dedicated team of support professionals and advocates.

- Education
- Health Insurance Navigation
- Community Connections
- Ongoing Support

OneSource™ is a complimentary, personalized patient support program offered by Alexion

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.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

Please see reverse for Indications and Important Safety Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis

[a]Adults and pediatric patients one month of age and older. [b]The mean (% coefficient of variation) terminal elimination half-life and clearance of ULTOMIRIS in patients with atypical-HUS are 51.8 (31.3) days and 0.08 (53.3) L/day, respectively. Half-life of eculizumab is 11.25 to 17.25 days.[1,2] [c]Targeted engineering to incorporate 4 amino acid substitutions designed to reduce TMDD and enhance FcRn-mediated recycling into eculizumab has led to the generation of ULTOMIRIS, which exhibited an extended duration of action in preclinical models relative to eculizumab.[3] [d]In all patients with PNH and the majority (93%) of adult and pediatric patients with atypical-HUS throughout the entire 26-week treatment period.[1] [e]Patient preference data from a sub-study of ULTOMIRIS PNH switch study extension period.

C5, complement component 5; gMG, generalized myasthenia gravis; HUS, hemolytic uremic syndrome; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal hemoglobinuria; TMDD, target-mediated drug disposition.

1. ULTOMIRIS [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; 2020. 2. Soliris [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; 2019. 3. Sheridan D, et al. *PLoS One*. 2018;13(4):e0195909 4. Data on file. Alexion Pharmaceuticals, Inc. 5. Peipert JD, et al. Poster presented at: Eur. Hematol. Assoc. Ann. Mtg. 2019; June 13-16, 2019; Amsterdam, Netherlands.

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

INDICATIONS & IMPORTANT SAFETY INFORMATION for ULTOMIRIS (ravulizumab-cwvz)

INDICATIONS

Paroxysmal Nocturnal Hemoglobinuria (PNH)

ULTOMIRIS is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Atypical Hemolytic Uremic Syndrome (aHUS)

ULTOMIRIS is indicated for 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).

Limitation of Use:

ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

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.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

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

Risk and Prevention

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. If ULTOMIRIS must be initiated immediately in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide 2 weeks of antibacterial drug prophylaxis. In clinical studies, 59 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 PNH clinical studies, 3 out of 261 PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS; all 3 had been vaccinated. These 3 patients recovered while continuing treatment with ULTOMIRIS. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

REMS

Under the ULTOMIRIS REMS, prescribers must enroll in the program due to the risk of meningococcal infections. 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.

Other Infections

Patients may have increased susceptibility to encapsulated bacteria infections, especially 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.

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

Treatment Discontinuation for PNH

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.

Treatment Discontinuation for aHUS

ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized. There are no specific data on ULTOMIRIS discontinuation. After discontinuing treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months.

TMA complications post-discontinuation can be identified if any of the following is observed: Clinical symptoms of TMA include changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure. In addition, at least two of the following laboratory signs observed concurrently and results should be confirmed by a second measurement 28 days apart with no interruption: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment. If TMA complications occur after discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.

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

Administration of ULTOMIRIS may result in infusion-related reactions. In clinical trials, 5 out of 296 patients treated with ULTOMIRIS experienced infusion-related reactions (lower back pain, drop in blood pressure, infusion-related pain, elevation in blood pressure and limbs discomfort) during ULTOMIRIS administration which did not require discontinuation. Interrupt infusion and institute supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

Adverse Reactions for PNH

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.

Adverse Reactions for aHUS

Most common adverse reactions in patients with aHUS (incidence $\geq$20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 42 (57%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were hypertension, pneumonia and abdominal pain. In clinical studies, clinically relevant adverse reactions in $<$10% of patients include viral tonsillitis in adults and viral infection in pediatric patients.

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

ALEXION®