ALEXION
AstraZeneca Rare Disease

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

Atypical-HUS Treatment Duration Considerations

This document is intended for healthcare professionals for educational purposes. The material contained within is not appropriate for use in continuing medical education (CME) content or programs.

INDICATION

ULTOMIRIS is indicated for the treatment of adult 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).

Subcutaneous Use in Adult Patients with aHUS

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

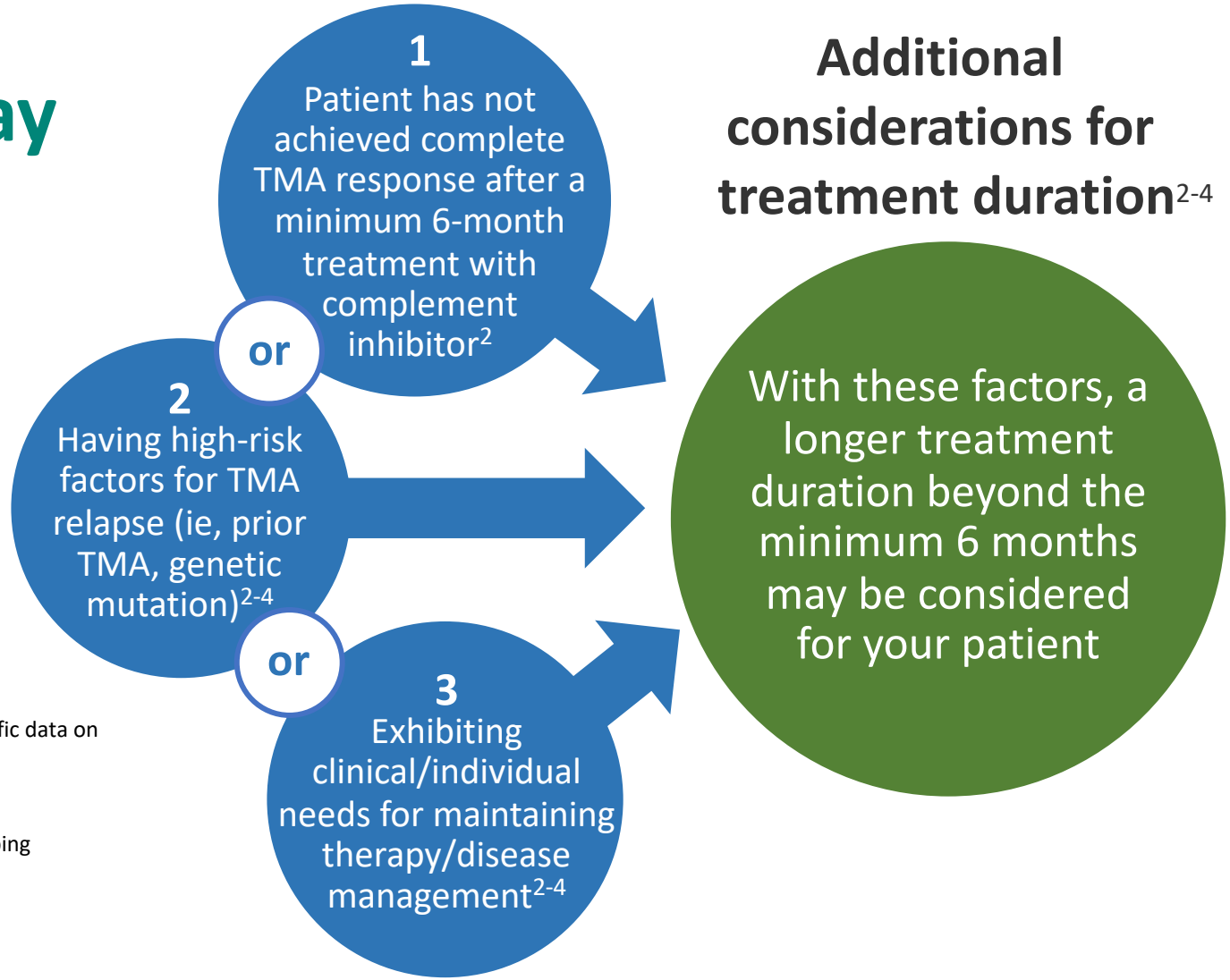
- Patients with unresolved *Neisseria meningitidis* infection.
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection.

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

Treatment duration may be individualized

A 13.5-fold higher rate of TMA was seen in patients who discontinued complement inhibitor therapy vs patients who stayed on therapy[1,a]

ULTOMIRIS Prescribing Information: ULTOMIRIS treatment of atypical-HUS should be a minimum duration of 6 months, after which treatment duration should be individualized



[a]In a long-term, prospective, observational study of eculizumab.[1] There are no specific data on discontinuation of ULTOMIRIS.[2]
TMA=thrombotic microangiopathy

References: 1. Menne J, et al. *BMC Nephrol*. 2019;20(1):125. **2.** ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **3.** Laurence J. *Clin Adv Hematol Oncol*. 2020;18(4):221-230. **4.** Fakhouri F, et al. *Clin J Am Soc Nephrol*. 2017;12(1):50-59.

Treatment duration may be individualized

Based on clinical judgment, including minimal TMA relapse risk and complete TMA response, discontinuation of ULTOMIRIS can be assessed

AFTER ULTOMIRIS DISCONTINUATION

Ongoing monitoring for TMA should be performed in your patients for at least 12 months[1]

- Laboratory and clinical signs of TMA should be closely monitored
- There are no specific data on ULTOMIRIS discontinuation
- In atypical-HUS, the risk of TMA complications may be lifelong[2]

If TMA complications occur after ULTOMIRIS discontinuation, consider reinitiating ULTOMIRIS treatment or initiating appropriate organ-specific supportive measures

TMA=thrombotic microangiopathy

References: 1. ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **2.** Asif A. *J Nephrol*. 2017;347-362.

Treatment duration may be individualized (cont'd)

Based on clinical judgment, including minimal TMA relapse risk and complete TMA response, discontinuation of ULTOMIRIS can be assessed

TIPS FOR IDENTIFYING TMA POST-DISCONTINUATION

Signs of clinical symptoms of TMA, including ≥25% change in at least 2 of the following[1,2,a]:

- ↓ platelet count[b]
- ↑ serum creatinine[c]
- ↑ serum LDH[c]

If TMA complications occur after ULTOMIRIS discontinuation, consider reinitiating ULTOMIRIS treatment or initiating appropriate organ-specific supportive measures[1]

[a]Observed concurrently and confirmed by a second measurement 28 days apart with no interruption
[b]Change from baseline or peak value during ULTOMIRIS treatment
[c]Change from baseline or nadir level during ULTOMIRIS treatment
LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy

References: 1. ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **2.** Laurence J. *Clin Adv Hematol Oncol.* 2020;18(4):221-230.

SELECT IMPORTANT SAFETY INFORMATION

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.

The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. 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.

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

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

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.

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

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.

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SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

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.

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SELECT IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Most common adverse reactions in patients with aHUS (incidence ≥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 and in 3% of adult patients include infusion-related reactions.

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.

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Contact Alexion

For more information on atypical-HUS or ULTOMIRIS, connect with a live representative by calling 833-551-2539 or emailing AlexionConnectTeam@alexion.com

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