AstraZeneca

ULTOMIRIS® (ravulizumab) PHYSICIAN'S GUIDE

Paroxysmal Nocturnal Hemoglobinuria (**PNH**)

Atypical Hemolytic Uremic Syndrome (**aHUS**)

Generalized Myasthenia Gravis (**gMG**)

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1 INTRODUCTION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients with:

Paroxysmal nocturnal hemoglobinuria (PNH):

- who present with clinical symptom(s) indicative of high disease activity.
- who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Atypical hemolytic uremic syndrome (aHUS):

- to inhibit complement-mediated thrombotic microangiopathy (TMA).
- Limitations of Use: ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS).

ULTOMIRIS is also indicated as an add-on to standard therapy for the treatment of adult patients with **generalized myasthenia gravis (gMG)** who are anti-acetylcholine receptor (AChR) antibody-positive.

This guide is intended to increase the prescriber's awareness of the risks associated with the use of ULTOMIRIS® which include meningococcal infection, serious infections, immunogenicity, and use in pregnant and breast-feeding women. It is also intended to increase the prescriber's awareness of the risks associated with discontinuation of ULTOMIRIS®.

This guide must be used in combination with the ULTOMIRIS® Singapore Package Insert (PI).

You will be provided with the following material to be given to each patient treated with ULTOMIRIS®:

- **Patient Safety Information Card**

  To inform patients and healthcare providers about the risk of meningococcal infection associated with ULTOMIRIS®
- **Patient/Parent/Legal Guardian Guide**

  To educate patients and parents/legal guardians of infants and children about the safety considerations associated with ULTOMIRIS® treatment

Read these materials ahead of prescribing ULTOMIRIS® to your patients.

2 IMPORTANT SAFETY INFORMATION[1]

Serious Meningococcal Infection

- Due to its mechanism of action, the use of ULTOMIRIS® increases the risk of meningococcal infection/sepsis (*Neisseria meningitidis*) for the patient.
- Cases of serious or fatal meningococcal infection/sepsis have been reported in ULTOMIRIS®-treated patients and with other terminal complement inhibitors. Meningococcal infections in patients treated with ULTOMIRIS® have presented as meningococcal sepsis or meningococcal encephalitis.

To minimise the risk of meningococcal infection and poor outcomes following infection:

Prior to starting treatment with ULTOMIRIS®:

- ▶ Vaccinate your patients with a meningococcal vaccine at least 2 weeks prior to initiating ULTOMIRIS®, unless the risk of delaying ULTOMIRIS® therapy outweighs the risk of developing a meningococcal infection. Vaccines against serogroups A, C, Y, W135, are recommended in preventing the commonly pathogenic meningococcal serogroups. Vaccine against serogroup B where available is also recommended.
  - For patients who initiate ULTOMIRIS® treatment less than 2 weeks after receiving a meningococcal vaccine, treat with appropriate prophylactic antibiotics for at least 2 weeks after vaccination.
- ▶ Monitor patients closely for disease symptoms after recommended vaccination as vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease, such as hemolysis (PNH), TMA (aHUS) or MG exacerbation (gMG).
- ▶ Since vaccination may not be sufficient to prevent meningococcal infection, consider prophylactic use of antibiotics in addition to vaccination based on the official guidance on the appropriate use of antibacterial agents.

During treatment with ULTOMIRIS®:

- ▶ Monitor your patients for early signs of meningococcal infections and sepsis, evaluate immediately if infection is suspected, and treat with antibiotics if necessary.
- ▶ Revaccinate according to current national vaccination guidelines for vaccine use in patients treated with complement inhibitors.

Do not initiate ULTOMIRIS® therapy in patients:

- with unresolved *Neisseria meningitidis* infection.
- who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

Please see the Singapore Package Insert (PI) for ULTOMIRIS®, including information regarding serious meningococcal infection.

Other Systemic Serious Infections

- Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infection, have been reported with ULTOMIRIS®. Advise patients about gonorrhea prevention.
- Vaccinate patients less than 18 years of age against *Haemophilus influenzae* and pneumococcal infections. Strict adherence to the national vaccination recommendations for each age group is needed.
- Administer ULTOMIRIS® therapy with caution to patients with active systemic infections.

Immunogenicity

- Treatment with any therapeutic protein may induce an immune response (e.g. development of anti-drug antibodies).
- Monitor your patients for any signs and symptoms associated with positive anti-drug antibodies.

Pregnancy and Lactation

- For ULTOMIRIS®, no clinical data on exposed pregnancies are available.
- Women of childbearing potential should use effective contraception during treatment and up to 8 months after treatment.
- Breastfeeding should be discontinued during treatment and up to 8 months after treatment.
- Male patients should not father a child or donate sperm up to eight months after treatment.

3 INFORMATION THAT YOU SHOULD PROVIDE TO PATIENTS AND PARENTS/ LEGAL GUARDIANS

Risk of meningococcal infection:

Inform and educate patients that if they suspect an infection, they should seek immediate medical attention.

The relevant signs and symptoms include:

- Headache with nausea or vomiting
- Headache and a fever
- Headache with a stiff neck or stiff back
- Fever
- Fever and a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eyes sensitive to light

Common Signs and Symptoms in infants include[2]:

- Fever, cold hands and feet
- Fretful, dislike being handled
- Rapid breathing or grunting
- Unusual cry, moaning
- Stiff neck, dislike bright lights
- Refusing food and vomiting
- Drowsy, floppy, unresponsive
- Pale, blotchy skin spots/rash
- Tense, bulging fontanelle (soft spot)
- Convulsions/seizures

In children, additional signs and symptoms to those listed for infants may include[3]:

- Severe muscle pain
- Severe headache
- Confusion
- Irritability

Explain to the patient that he/she needs to carry the Patient Safety Information Card at all times throughout the duration of ULTOMIRIS® therapy and for 8 months after the last dose of ULTOMIRIS® and show it to any healthcare professionals they see.

Please see the Singapore Package Insert (PI) for ULTOMIRIS®, including information regarding serious meningococcal infection.

4 TREATMENT DISCONTINUATION[1]

Treatment discontinuation in PNH

Closely monitor patients with PNH who discontinue ULTOMIRIS® for signs and symptoms of hemolysis and other reactions for at least 16 weeks.

These are identified by:

1. Elevated LDH (lactate dehydrogenase)

   AND

2. any of the following

   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
   - erectile dysfunction

If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS®.

Treatment discontinuation in aHUS

Monitor aHUS patients who discontinue treatment with ULTOMIRIS® for signs and symptoms of thrombotic microangiopathy (TMA).

TMA complications following discontinuation can be identified by:

1. at least two of the following laboratory results observed concurrently:
   - 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;

   (results should be confirmed by a second measurement 28 days apart)

   OR
2. any one of the following symptoms of TMA:
   - a change in mental status or seizures;
   - other extra renal TMA manifestations including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhea; or,
   - thrombosis.

If TMA complications occur after discontinuation, consider reinitiation of ULTOMIRIS® treatment beginning with the loading dose and maintenance dose.

Treatment discontinuation in gMG

Considering that gMG is a chronic disease, patients benefiting from ULTOMIRIS® treatment who discontinue treatment should be monitored for symptoms of the underlying disease.

If symptoms of gMG occur after discontinuation, consider restarting treatment with ULTOMIRIS®.

Please see the Singapore Package Insert (PI) for ULTOMIRIS®, including information regarding serious meningococcal infection.

FURTHER INFORMATION

For more information about ULTOMIRIS®, email: MedInfo.SG@astrazeneca.com.

Adverse events should be reported to: PatientSafety.SG@astrazeneca.com.

Company address:

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This document has been approved by Singapore Health Sciences Authority (HSA) on 19-JUN-2024.

REFERENCES

1. ULTOMIRIS® Singapore Package Insert (PI).
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3. Signs and symptoms of meningitis in babies and toddlers. Meningitis Now website. Available at: https://www.meningitisnow.org/meningitis-explained/signs-and-symptoms/signs-and-symptoms-babies-and-toddlers/ (Accessed: 04 November 2022).
4. Meningitis symptoms in children. Meningitis Now website. Available at: https://www.meningitisnow.org/meningitis-explained/signs-and-symptoms/signs-and-symptoms-children/ (Accessed: 04 November 2022).

NOTES

Please see the Singapore Package Insert (PI) for ULTOMIRIS®, including information regarding serious meningococcal infection.