ALEXION
AstraZeneca Rare Disease

ULTOMIRIS® ▼ (ravulizumab)
PHYSICIAN'S GUIDE

Paroxysmal Nocturnal Haemoglobinuria **(PNH)**

Atypical Haemolytic Uremic Syndrome **(aHUS)**

Generalized Myasthenia Gravis **(gMG)**

Neuromyelitis Optica Spectrum Disorder **(NMOSD)**

▼ This medicinal product is subject to additional monitoring.
This will allow quick identification of new safety information.

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1 INTRODUCTION

Ravulizumab is indicated:

- in the treatment of adult and paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria **(PNH)**
  - in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
  - in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.
- in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome **(aHUS)** who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.
- 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.
- in the treatment of adult patients with neuromyelitis optica spectrum disorder **(NMOSD)** who are anti-aquaporin 4 (AQP4) antibody-positive.

This guide is intended to increase the prescriber's awareness of the risks associated with the use of ravulizumab, which include: meningococcal infection, serious infections, immunogenicity, malignancies, and haematological abnormalities in PNH patients, 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 ravulizumab.

This guide must be used in combination with the ravulizumab Summary Of Product Characteristics (SmPC).

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

- **Patient Alert Card**

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

  To educate patients, parents/legal guardians of infants and children and healthcare providers about the safety considerations associated with ravulizumab treatment.
- **Patient Information leaflet**

Read these materials ahead of prescribing ravulizumab to your patients.

2 IMPORTANT SAFETY INFORMATION[1]

Serious Meningococcal Infection

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

- Vaccinate your patients with a meningococcal vaccine at least 2 weeks prior to initiating ravulizumab, unless the risk of delaying ravulizumab 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 ravulizumab 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.
- Since vaccination may not suffice 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 ravulizumab:

- 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.

Other Systemic Serious Infections

- Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infection, have been reported with ravulizumab. Advise patients about gonorrhoea 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 ravulizumab 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 the patients for any signs and symptoms associated with positive anti-drug antibodies.

Haematologic Abnormality and Malignancy

- Due to the natural evolution of the disease, there is a risk for patients with PNH to develop haematologic abnormalities or malignancies, such as aplastic anaemia or myelodysplastic syndrome. The potential role of ravulizumab in such abnormalities or malignancies has not been studied.
- Patients with PNH should be monitored for haematological changes.

Pregnancy and Lactation

- For ravulizumab, no clinical data on exposed pregnancies are available. Ravulizumab should be given to a pregnant woman only if clearly needed.
- Women of childbearing potential must 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 WHAT YOU NEED TO INFORM 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:

- 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:

- Severe muscle pain
- Severe headache
- Confusion
- Irritability

Explain to the patient the necessity to carry the patient card at all times throughout the duration of ravulizumab therapy and for 8 months after the last dose of ravulizumab. Also, explain that they should show it to any healthcare professionals they see.

4 TREATMENT DISCONTINUATION[1]

Treatment discontinuation for PNH:

Closely monitor patients with PNH who discontinue ravulizumab for signs and symptoms of haemolysis 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 haemoglobin

   or

   reappearance of symptoms, such as;
   - fatigue
   - haemoglobinuria
   - abdominal pain
   - shortness of breath dyspnoea
   - major adverse vascular event (including thrombosis)
   - dyspnoea
   - erectile dysfunction

If signs and symptoms of haemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ravulizumab.

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Treatment discontinuation for aHUS

Monitor aHUS patients who discontinue treatment with ravulizumab 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 ravulizumab treatment
- an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ravulizumab treatment
- an increase in serum LDH of 25% or more as compared to baseline or to nadir during ravulizumab treatment (results should be confirmed by a second measurement)

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/diarrhoea
- thrombosis

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

REPORTING ADVERSE DRUG REACTIONS

Reporting suspected adverse drug reactions (ADRs) after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Malta Medicines Authority

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to; P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 E: postlicensing.medicinesauthority@gov.mt

Alexion Pharma

Adverse events should also be reported to Alexion Pharma at www.contactazmedical.astrazeneca.com

MORE INFORMATION

For more information about ravulizumab contact: medinfo.EMEA@alexion.com

REFERENCES

1. ULTOMIRIS® (ravulizumab) SmPC, available here: www.ema.europa.eu