ALEXION
AstraZeneca Rare Disease

ULTOMIRIS® (ravulizumab)
PHYSICIAN'S GUIDE

Paroxysmal Nocturnal Haemoglobinuria (**PNH**)

Atypical Hemolytic 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.

TABLE OF CONTENTS

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 Guide and Parent/Legal Guardian Guide**
  To educate patients and 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 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 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 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 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), which may results in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis).
- Patients should be monitored post-infusion for any signs and symptoms of reactions.
- In case of infusion reactions, infusion of ravulizumab should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.

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

Inform the patient about the PNH/aHUS Registry and how to participate. <u>This is only open to patients in Great Britain.</u>

Inform PNH and aHUS patients about the respective patient disease registry and how to participate. The aim of the **PNH and aHUS registries** is to collect data to characterise the progression of these diseases as well as the associated clinical outcomes, mortality and morbidity. Accumulating results from the PNH and aHUS Registries may provide a better understanding of these diseases and their real-world outcomes. Information can also be requested from ClinicalTrials@alexion.com (please include the subject line: NCT01374360, M07-001, paroxysmal nocturnal haemoglobinuria (PNH) Registry or NCT01522183, atypical haemolytic uremic syndrome (aHUS) Registry).

Should you wish for your patient to participate in the PNH registry, please refer the patient to the UK PNH service centres where the service team will direct you to one of the active registry sites. More information about the location of UK aHUS Registry sites can be obtained by contacting Alexion directly. At the active registry centres PNH and aHUS patients will receive more detailed information about the respective disease registry and will be asked to sign a consent form with a qualified investigator if they wish to participate. Patients will need to complete a simple questionnaire about their health and well-being at the beginning, and then every 6 months for the duration of the Registry.

The purpose of the questionnaire is to obtain the patient's views about their general health, well-being, and treatment received. You will be required to provide the patient's medical information such as diagnosis, treatment and medical history. All patient information that is provided to either the PNH or aHUS Registry will be kept confidential and pseudonymised.

4 TREATMENT DISCONTINUATION[1]

Treatment discontinuation for PNH:

Closely monitor patients with PNH who discontinue ravulizumab for signs and symptoms of haemolysisand 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 ravulizumab.

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; or,
    - 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 reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions.

United Kingdom (Great Britain and Northern Ireland)

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. Reporting forms and information can be found at www.yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Alexion Pharma UK Ltd on uk.adverseevents@alexion.com or Freephone (UK): 0800 321 3902

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

Adverse events should also be reported to Alexion Pharma UK Ltd on uk.adverseevents@alexion.com or Freephone (UK): 0800 321 3902

MORE INFORMATION

For more information about ravulizumab contact: medinfo.EMEA@alexion.com
Tel: UK: 0800 028 4394/ Ireland: 1800 882 840

HOME HEALTHCARE SERVICES

Alexion funds a Home Healthcare service, which is available to all patients prescribed with ravulizumab. For more details, please contact your local Alexion office via customeroperationsuk@alexion.com or Tel: 0800 130 0212.

REFERENCES

1. ULTOMIRIS® (ravulizumab) SmPC, available here: https://www.medicines.org.uk/emc/, https://www.emcmedicines.com/en-GB/northernireland/ or https://www.medicines.ie/