ULTOMIRIS® ▼ (ravulizumab)

Physician's Guide

Important information for patients about serious adverse events or reactions

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

ALEXION®
AstraZeneca Rare Disease

Ultomiris_Physician Guide_V14 Revised January 2023

RAVULIZUMAB SAFETY PROFILE[1]

The aim of this brochure is to inform and/or remind healthcare professionals about the selected prevention measures, detection, careful monitoring and/or proper management of selected safety concerns associated with ravulizumab to minimise the risk of serious side effects. The brochure is for prescribers who are treating patients with one of the following conditions: 1) paroxysmal nocturnal haemoglobinuria (PNH), 2) atypical haemolytic uraemic syndrome (aHUS), or 3) Generalised Myasthenia Gravis (gMG).

IMPORTANT SAFETY INFORMATION[1]

Meningococcal Infection

Due to its mechanism of action, the use of ravulizumab increases the risk of meningococcal infection (*Neisseria meningitidis*) for the patient.

The following steps must be taken to minimise the risk of meningococcal infection and the risk of poor outcomes following infection.

Provide your patients with meningococcal vaccinations and/or prophylactic antibiotics as explained below:

- **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 and B** (where available) are recommended.
- **Vaccination or revaccination** may further activate complement and, as a result, patients with complement-mediated diseases **may experience increased signs and symptoms of their underlying disease**.
- **Revaccinate** according to current national vaccination guidelines for vaccine use.
- Patients who have not been vaccinated prior to initiating ravulizumab treatment should receive **prophylactic antibiotics** prior to and **for at least 2 weeks** after meningococcal vaccination.

- **Monitor** your patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary.
- **Provide a Patient/Parent Guide** (to patients/parents). **Explain the guide** to parents and/or patients being treated with ravulizumab in order to increase their awareness of potential meningococcal infections and the relevant signs and symptoms which 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

- **Alert** parents/legal guardians of paediatric patients of varying signs and symptoms of meningitis/sepsis in different age groups - infants and children. Refer parents/legal guardians to the Parent Guide.
- **Provide a Patient Alert Card** to patients or parents/legal guardians of paediatric patients being treated with ravulizumab and explain that they must carry it at all times while on ravulizumab treatment and for 8 months after last dose and show it to healthcare professionals they see.
- **Inform patients that if they suspect they may have an infection, they should seek urgent medical advice.**
- **Explain the purpose of paroxysmal nocturnal haemoglobinuria (PNH)/atypical haemolytic uremic syndrome (aHUS) Registries and how patients are entered into the relevant PNH/aHUS Registry.**

IMPORTANT SAFETY INFORMATION[1] *(cont.)*

Immunogenicity:

Treatment with any therapeutic protein may induce an immune response (e.g. development of anti-drug antibodies), which may result 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 reaction, infusion of ravulizumab should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.

Haematological Abnormalities and Malignancies:

Physicians are reminded that PNH patients should be monitored for haematological changes. This includes PNH patients treated with ravulizumab, where PNH laboratory monitoring should potentially alert physicians to haematological abnormalities and malignancies during ravulizumab treatment, and for a period not less than 16 weeks after ravulizumab discontinuation.

Risk of haemolysis:

After ravulizumab discontinuation in PNH patients there may be a risk of serious haemolysis (*see section on treatment discontinuation*).

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients in ravulizumab.
- Patients with unresolved *Neisseria meningitidis* infection at treatment initiation.
- Patients who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

Pregnant and Breast-feeding Women:

There are no clinical data for the use of ravulizumab in pregnant women. In pregnant women the use of ravulizumab may be considered following an assessment of the risks and benefits. Women of childbearing potential must use effective contraception during treatment and up to 8 months after treatment.

Breast-feeding should be discontinued during treatment and up to 8 months after treatment. Male patients on ravulizumab, should not father a child or donate sperm up to 8 months after treatment.

Other Systemic Infections:

Ravulizumab therapy should be administered with caution to patients with active systemic infections. Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported with ravulizumab.

Physicians should advise patients about gonorrhoea prevention.

STARTING YOUR PATIENT ON RAVULIZUMAB[1]

IMPORTANT INFORMATION

Vaccination/Prophylaxis antibiotic Certificate

In order to minimise the risk of inappropriate use of ULTOMIRIS (ravulizumab), the Decision of the European Commission and the follow-up measures agreed by the CHMP require that drug distribution by Alexion will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis is submitted by the prescriber to Alexion Pharma UK.

For UK and Channel Islands.
CustomerOperationsUK@Alexion.com

For Ireland, Northern Ireland and Malta.
CustomerOperationsUK@Alexion.com

Alexion will not be able to process any orders for patients for which we have not received the Vaccination/Prophylaxis antibiotic Certificate.

We therefore ask you to enter the patient code and the birthdate of the patient for whom the drug is purchased, on any future orders for ravulizumab, in order to verify the correspondence with the Vaccination/Prophylaxis antibiotic Certificate. Alexion will not be able to process any orders for patients for which we have not received a completed Vaccination/Prophylaxis antibiotic Certificate.

To successfully start your patient on ravulizumab, there are some steps you need to take:

- **Vaccinate** your patient against *Neisseria meningitidis* (*see section on important safety information*). Patients under 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections. Strict adherence to the national vaccination recommendations for each age group is needed.
- **Inform and educate** about the risk of meningococcal infection to your patient, or the parent/legal guardian of your patient being treated with ravulizumab (*see section on important safety information*).

– Explain why patients must be vaccinated before starting the treatment and the need to be revaccinated.

– Explain why they should be on antibiotic prophylaxis if ravulizumab is initiated less than 2 weeks before vaccination or they are unable to be vaccinated.

– Provide a Patient Alert Card to patients or parent/legal guardian of paediatric patients. Explain that they must carry it at all times while on ravulizumab treatment and for 8 months after last dose and must show it to healthcare professionals.

– Train them to recognise signs and symptoms of meningococcal infection and to seek medical attention.

- Provide a Patient Guide to patients. Parents/legal guardians of paediatric patients shall receive in addition a Parent Guide. Make sure your patient treated with ravulizumab or the parent/legal guardian of paediatric patients understands the information given.
- Warn them about the risk of interrupting treatment (*see section on treatment discontinuation*).
- Plan and agree on a dosing appointment schedule with the patient treated with ravulizumab, or the parent/legal guardian of paediatric patients.

To help you start your patient on ravulizumab, you will be provided a "starter kit" to give to each patient treated with ravulizumab to give important information about this treatment.

THIS STARTER KIT COMPRISES:

- **Patient Guide: provides your patient with important safety information regarding ravulizumab, the potential side effects of the treatment, and safety warnings.**
- **Parent Guide: provides important safety information regarding ravulizumab for parents/legal guardians of young children on ravulizumab.**
- **Patient Alert Card: specifies that the person carrying it is under ravulizumab treatment; the physician's name and telephone number are also included. Your patient must carry this card at all times while on ravulizumab and for 8 months after last dose.**
- **Summary of medicinal Product Characteristics and Patient information leaflet for Ultomiris (containing ravulizumab).**

PNH and aHUS REGISTRIES

Inform PNH and aHUS patients about the disease registries in Great Britain and how to participate.

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.

TREATMENT DISCONTINUATION[1]

Since PNH, aHUS and gMG are chronic diseases, ravulizumab is intended as an ongoing therapy. Patients who start ravulizumab should continue receiving ravulizumab, even if they feel better. Interrupting or stopping treatment may cause your symptoms to come back after stopping ravulizumab.

YOU MUST NOT STOP TREATMENT WITHOUT MEDICAL SUPERVISION.

RISK OF SERIOUS INTRAVASCULAR HAEMOLYSIS AFTER DRUG DISCONTINUATION IN PATIENTS WITH PNH

If patients with PNH discontinue treatment with ravulizumab, they should be closely monitored for signs and symptoms of serious intravascular haemolysis, identified by:

- **Elevated LDH (lactate dehydrogenase) levels along with sudden decrease in PNH clone size or haemoglobin, or re-appearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction.**
- **Any patient who discontinues ravulizumab should be monitored for at least 16 weeks to detect haemolysis and other reactions.**
- **If signs and symptoms of haemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ravulizumab, beginning with the loading dose and maintenance dose.**

RISK OF RECURRENCE OF THROMBOTIC MICROANGIOPATHY (TMA) SYMPTOMS AFTER DRUG DISCONTINUATION IN PATIENTS WITH aHUS

aHUS patients who must discontinue treatment with ravulizumab should be monitored for signs and symptoms of TMA on an ongoing basis. However, monitoring may be insufficient to predict or prevent severe TMA complications.

TMA complications post-discontinuation can be identified if any of the following is observed:

1. At least two of the following laboratory results observed concurrently: a decrease in platelet count of ≥25% compared with either baseline or peak platelet count during ravulizumab treatment; an increase in serum creatinine of ≥25% compared with baseline or nadir during ravulizumab treatment; or, an increase in serum LDH of ≥25% compared with baseline or 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, or other extra renal TMA manifestations including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/ diarrhoea; or thrombosis

IF TMA COMPLICATIONS OCCUR AFTER RAVULIZUMAB DISCONTINUATION, CONSIDER THE RE-INITIATION OF RAVULIZUMAB TREATMENT BEGINNING WITH THE LOADING DOSE AND MAINTENANCE DOSE (refer to Section 4.2 of SmPC).

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. You can report via:

- the Yellow Card website www.mhra.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

Adverse events should also be reported to Alexion Pharma UK Ltd on uk.adverseevents@alexion.com
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
Freephone (Ireland): 1800 936 544

MORE INFORMATION

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

Tel: UK: 0800 028 4394/ Ireland: 1800 882 840

HOME HEALTHCARE SERVICE

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) Summary of Product Characteristics, available here: https://www.medicines.org.uk/emc/, https://www.emcmedicines.com/en-GB/northernireland/ or https://www.medicines.ie/