ALEXION
AstraZeneca Rare Disease

SOLIRIS® (eculizumab) PHYSICIAN'S GUIDE

Paroxysmal Nocturnal Haemoglobinuria **(PNH)**

Atypical haemolytic Uremic Syndrome **(aHUS)**

Refractory Generalized Myasthenia Gravis **(gMG)**

Neuromyelitis Optica Spectrum Disorder **(NMOSD)**

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1 INTRODUCTION

Eculizumab is indicated in adults and children for the treatment of:

- Paroxysmal nocturnal haemoglobinuria **(PNH)**

  Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.
- Atypical haemolytic uremic syndrome **(aHUS)**
- Refractory generalized myasthenia gravis **(gMG)** in patients aged 6 years and above who are anti-acetylcholine receptor (AChR) antibody-positive.

Eculizumab is **also** indicated in adults for the treatment of:

- Neuromyelitis optica spectrum disorder **(NMOSD)** in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease.

This guide is intended to increase the prescriber's awareness of the risks associated with the use of eculizumab which include meningococcal infections, serious infections (including sepsis), aspergillus infection, infusion reactions and immunogenicity. It is also intended to increase the prescriber's awareness of the risks associated with discontinuation of eculizumab.

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

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

- **Patient Alert Card**

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

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

Read these materials ahead of prescribing eculizumab to your patients.

2 IMPORTANT INFORMATION

Vaccination / Prophylaxis Antibiotic Certificate

In order to minimise the risk of inappropriate use of eculizumab, 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 has effectively received meningococcal vaccination and / or antibiotic prophylaxis.

For UK, Channel Islands and Malta:
CustomerOperationsUK@Alexion.com
Fax 0800 633 5145

For Ireland:
CustomerOperationsUK@Alexion.com
Fax 1800 995 100

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 eculizumab, in order to verify the correspondence with the Vaccination / Prophylaxis Antibiotic Certificate.

3 IMPORTANT SAFETY INFORMATION[1]

Serious Meningococcal Infection

- Due to its mechanism of action, the use of eculizumab increases the risk of meningococcal infection (*Neisseria meningitidis*) for the patient.
- Cases of serious or fatal meningococcal infection have been reported in eculizumab treated patients. Meningococcal infections in patients treated with eculizumab have presented as meningococcal sepsis.

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

Prior to starting treatment with eculizumab:

- ▶ Vaccinate your patients with a meningococcal vaccine at least 2 weeks prior to initiating eculizumab unless the risk of delaying eculizumab 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 eculizumab treatment less than 2 weeks after receiving a tetravalent meningococcal vaccine, treat with appropriate prophylactic antibiotics until 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, including PNH, aHUS, refractory gMG, and NMOSD, 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 eculizumab:

- ▶ Monitor your patients for early signs of meningococcal infections, 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 Infections

- Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infection, have been reported with eculizumab. Counsel patients about gonorrhea prevention and advise regular testing for patients at risk.
- 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 eculizumab therapy with caution to patients with active systemic infections.

Aspergillus Infection

- Cases of Aspergillus Infections, some of them fatal, have been reported in eculizumab treated patients.
- Eculizumab should be administered with caution to patients with active systemic infections, including Aspergillus infections.
- Increased awareness of the underlying risk factors to develop an Aspergillus infection such as immunosuppressive therapies, long term steroid use, severe pancytopenia, exposure to construction or demolition sites, and pre–existing lung impairment or Aspergillus infection is helpful in minimising the impact of the risk.
- Consider the patient's risk factors and adapt your surveillance and/or patient's underlying immunosuppressive treatment as feasible to mitigate the risk.

Infusion Reactions

- Administration of eculizumab may result in infusion reactions that could cause allergic or hypersensitivity reactions (including anaphylaxis).
- Monitor patients for one hour following infusion.
- Eculizumab administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy should be administered.

Immunogenicity

- Infrequent antibody responses have been detected in eculizumab treated patients across clinical studies.
- Monitor the patients for any signs and symptoms associated with positive anti-drug antibodies.

4 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 Alert Card at all times throughout the duration of eculizumab therapy and for 3 months after the last dose of eculizumab and show it to any healthcare professionals they see.

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

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 disease 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 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.

5 TREATMENT DISCONTINUATION[1]

Treatment discontinuation for PNH

Closely monitor patients with PNH who discontinue eculizumab for signs and symptoms of serious intravascular haemolysis and other reactions for at least 8 weeks.

Serious haemolysis is identified by:

1. Serum lactate dehydrogenase (LDH) greater than pre-treatment LDH

AND

2. Any of the following criteria:

- PNH clone size absolute↓ of > 25% (in the absence of dilution due to transfusion) in 1 week or less
- Hb < 5 g/dL OR Hb ↓ of > 4 g/dL in 1 week or less
- Angina
- Change in mental status
- Serum creatinine ↑ of 50%
- Thrombosis

If serious haemolysis occurs, consider the following procedures/treatment:

Blood transfusion (packed RBCs) OR Exchange transfusion if PNH RBCs>50% of total RBCs by flow cytometry + Anticoagulation + Corticosteroids OR Reinstitution of eculizumab

Treatment discontinuation for aHUS

Severe Thrombotic microangiopathy (TMA) complications were observed after eculizumab discontinuation in the aHUS clinical studies.

Monitor aHUS patients who discontinue treatment with eculizumab for signs and symptoms of TMA.

TMA complications following discontinuation can be identified by:

1. Any two, or repeated measurement of any one of the following:
   - a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during eculizumab treatment;
   - an increase in serum creatinine of 25% or more as compared to baseline or to nadir during eculizumab treatment; or,
   - an increase in serum LDH of 25% or more as compared to baseline or to nadir during eculizumab treatment;

   OR

2. Any one of the
   - a change in mental status or seizures;
   - angina or dyspnoea; or
   - thrombosis.

If severe thrombotic microangiopathy complications occur after eculizumab discontinuation, consider reinstitution of eculizumab treatment supportive care with PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion), or appropriate organ-specific supportive measures including renal support with dialysis, respiratory support with mechanical ventilation or anticoagulation.

Treatment Discontinuation in gMG

Use of eculizumab in refractory gMG treatment has been studied only in the setting of chronic administration. Carefully monitor patients who discontinue eculizumab treatment for signs and symptoms of disease exacerbation.

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 https://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

Health Products Regulatory Authority (HPRA)
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland, D02 XP77

Reporting forms and information can be found at www.hpra.ie, or email: medsafety@hpra.ie.

Adverse events should also be reported to Alexion Pharma UK Ltd on uk.adverseevents@alexion.com or Freephone: 1 800 936 544

More Information

For more information about eculizumab contact: medinfo.EMEA@alexion.com or 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 eculizumab. For more details, please contact your local Alexion office via customeroperationsuk@alexion.com or Tel: 0800 130 0212.

REFERENCES

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