BEKEMV® ▼(eculizumab)

Physician's Guide

Important information for healthcare providers about serious adverse events or reactions with BEKEMV (eculizumab)

▼ You can help by reporting any side effects via the instructions given in section "Reporting Adverse Drug Reactions"

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The aim of this brochure is to educate and/or remind healthcare professionals about the selected prevention measures, detection, careful monitoring and/or proper management of selected safety concerns associated with eculizumab.

This guide should be used in conjunction with the Summary of Product Characteristics for BEKEMV (eculizumab).

You will receive the following documents to be given to all patients treated with BEKEMV:

- **Patient Card:** Provides information to patients and healthcare professionals about the risks of meningococcal infection associated with BEKEMV and the sorbitol content warning.
- **Patient/Parent Information Guide:** Provides information to patients and parents/guardians about BEKEMV.
- **Package Leaflet**

IMPORTANT INFORMATION

Vaccination/Prophylaxis antibiotic Certificate

In order to minimize the risk of inappropriate use of eculizumab, distribution of the medicinal product is only possible after your written confirmation at the 1st order that you as the hospital understand that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis.

Eculizumab

The active drug substance in BEKEMV, is a recombinant humanised monoclonal antibody targeting the complement protein C5.

Eculizumab is a terminal complement inhibitor that prevents the generation of the terminal complement complex C5b-9. The early components of complement activation essential for opsonisation of microorganisms, initiation of immune response (both humoral and cellular) and clearance of immune complexes are preserved.

ECULIZUMAB INDICATION

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).

IMPORTANT SAFETY INFORMATION

Information for patients with Hereditary Fructose Intolerance (HFI3)

Eculizumab is contraindicated in patients with hereditary fructose intolerance (HFI) regardless of their age, and in babies and children under 2 years of age who may not yet be diagnosed with HFI. Please see sorbitol content warning on page 8.

Risk of severe MENINGOCOCCAL infection and sepsis

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

- Sepsis is a common presentation of meningococcal infections in patients treated with eculizumab.
- Monitor your patients for early signs of meningococcal infections.
- Evaluate immediately if infection is suspected, and treat with antibiotics if necessary.

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

***Neisseria meningitidis:* Vaccination and antibiotic prophylaxis**

- Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving eculizumab unless the risk of delaying eculizumab therapy outweighs the risks of developing a meningococcal infection.
- Vaccines against serogroups A, C, Y, W 135 and B (where available) are recommended. preventing the commonly pathogenic meningococcal serogroups. Vaccine against serogroup B where available is also recommended.
- Vaccinate according to current national vaccination guidelines for vaccine use.[2]
- Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
- All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary.
- Patients who start treatment with BEKEMV less than 2 weeks after receiving vaccination should be treated with antibiotic prophylaxis until 2 weeks after the vaccination can be given.
- Repeat vaccination according to current national guidelines for vaccination of patients treated with complement inhibitors

Impact of vaccination on underlying disease

- Vaccination (or revaccination) may further activate complement, As a result, patients with complement-mediated diseases, including PNH and aHUS, may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH) and thrombotic microangiopathy TMA (aHUS). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination

- Information to provide to patients on the risk of meningococcal infection
- **Provide the Patient/Parent Information Brochure. Explain the brochure** content to patients or parents/ caregivers of patients being treated with **eculizumab** in order to increase their awareness of potential serious infections and the relevant signs and symptoms which include:

- Headache with nausea or vomiting
- Headache with a stiff neck or back
- Fever
- Rash
- Confusion
- Severe muscle ache combined with flu-like symptoms
- Sensitivity to light

In children additional signs and symptoms to those listed above may include:

- Rapid breathing
- Cold hands and feet
- Refusing food and/or vomiting
- Unusual crying or moaning
- Stiff neck
- Being drowsy or difficult to wake
- Irritability
- Shaking and leg pain

Provide a Patient Safety Card to patients being treated with **eculizumab** and explain that they must carry it at all times and for 3 months after last dose and show it to healthcare professionals they see.

- Physicians must discuss the benefits and risks of eculizumab therapy with patients/parents.
- **Inform patients that if they/their child suspect they may have an infection, they should seek urgent medical advice/caregivers.**
- Phyaicians must also explain:
  - **the requirement for vaccinations and/or antibiotic prophylaxis before starting treatment with BEKEMV**
  - **the risks of serious metabolic harms to patients with HFI if they are exposed to intravenous sorbitol (sorbitol is included in BEKEMV's formulation)**

Ensure that the parents/legal guardians can confidently identify typical symptoms of headache, fever, and neck stiffness which may be hard to detect in younger children, so train them to be aware of other symptoms including inactivity, irritability, vomiting, and poor feeding and to seek urgent medical attention.

Other systemic infections

Haemophilus influenzae and pneumococcal infections

Vaccinate patients less than 18 years against Haemophilus influenzae and pneumococcal infections according to national vaccination guidelines prior to initiation of BEKEMV therapy and strictly adhere to the national vaccination recommendations for each age group.

Neisseria species infections

Due to its mechanism of action, eculizumab therapy should be administered with caution to patients with active systemic infections (particularly due to *Neisseria* and encapsulated bacteria). Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

Physicians should advise patients about gonorrhoea prevention, based on advice for prevention of other sexually transmitted infections that includes use of appropriate barrier contraception and condoms in sexually active patients.

Aspergillus infection

Cases of *Aspergillus* infections, some of them fatal, have been reported in eculizumab-treated patients.

Underlying risk factors such as, long term steroid use, immunosuppressive treatments, severe pancytopenia, exposure to construction or demolition sites, and pre–existing lung impairment or *Aspergillus* infection should be considered. If one of the above risk factors is identified before starting treatment with eculizumab, appropriate measures to mitigate the risk of *Aspergillus* infection are advisable.

OTHER SERIOUS ADVERSE REACTIONS

Infusion reactions including anaphylaxis

As with all therapeutic proteins, administration of eculizumab may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis).

Patients should be monitored for one hour following infusion. If an adverse event occurs during the administration of eculizumab, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed two hours in and four hours in paediatric patients under 18 years of age.Immunogenicity

Immunogenicity

Infrequent antibody responses have been detected in eculizumab-treated patients across clinical studies. There has been no observed correlation of antibody development to clinical response or adverse events.

SORBITOL CONTENT WARNING

Each ml of this medicinal product contains 50 mg of sorbitol (E420). Patients with hereditary fructose intolerance (HFI[3]) must not take this medicine. In HFI[3] patients more than 2 years old, a spontaneous aversion for fructose-containing foods develops and may be combined with the onset of symptoms (vomiting, gastrointestinal disorders, apathy, height and weight retardation). Therefore, a detailed history with regard to HFI[3] symptoms has to be taken of each patient prior to receiving BEKEMV.

After intravenous administration of a sorbitol-containing medicine like BEKEMV, patients with HFI[3] may present with hypoglycemia, metabolic acidosis, seizures, or coma, all of which may be life-threatening. In case of inadvertent administration to a patient with known or suspected fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care. Chronic exposure to sorbitol in patients with HFI[3] may cause failure to thrive, kidney failure, and liver failure.

Babies and children (below 2 years of age) may not yet be diagnosed with HFI[3]. Medicines containing sorbitol/fructose given intravenously may be life-threatening and must be contraindicated in this population.

RISKS ASSOCIATED WITH DISCONTINUATION OF eculizumab

Patients with PNH

Serious intravascular haemolysis

Patients who start eculizumab as treatment for PNH should continue receiving eculizumab, even if they feel better.

However, patients who discontinue treatment with eculizumab should be monitored for signs and symptoms of serious intravascular haemolysis and other reactions for at least 8 weeks. There is serious haemolysis when serum LDH is greater than pre-treatment LDH and patients have any of the following criteria: greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in one week or less; a haemoglobin level of < 5 g/dL or a decrease of > 4 g/dL in one week or less; angina; change in mental status; a 50% increase in serum creatinine level; or thrombosis.

If serious haemolysis occurs, consider the following procedures/treatments: blood transfusion (packed RBCs) or exchange transfusion if PNH RBCs >50% of total RBCs by flow cytometry; anticoagulation; corticosteroids, or reconstitution of eculizumab.

Patients with aHUS

Severe Thrombotic microangiopathy (TMA)

Patients who start eculizumab as treatment for aHUS should continue receiving eculizumab, even if their condition appears to have improved.

Complications associated with severe thrombotic micorangiopathy (TMA) have been observed after discontinuation of treatment with eculizumab-treated patients in the aHUS clinical trials.

Patients discontinuing BEKEMV should be closely monitored for signs and symptoms of TMA. These may include:

- Two of the following or repeated measurements of one of the following:
    - o A reduction in platelet count of 25% or more compared to baseline or peak platelet count during treatment with BEKEMV
    - o An increase in serum creatinine of 25% or more compared to baseline or to nadir during treatment with BEKEMV
    - o An increase in serum LDH of 25% or more compared to baseline or to nadir during treatment with BEKEMV

OR

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

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

Please refer to the SPC for further information

REPORTING ADVERSE DRUG REACTIONS

Contact details for adverse event reporting or to request further information. Any suspected adverse reactions should be reported immediately to local Amgen safety contacts or the National Pharmacovigilance Center

Amgen Local Safety Contacts
Tel: +966 112 799328
E-mail: safety-mea@amgen.com

The National Pharmacovigilance Centre (NPC)
Saudi Food and Drug Authority (SFDA)
SFDA call center 19999
E-mail: npc.drug@sfda.gov.sa Online: http://ade.sfda.gov.sa/

Should you have any questions or require additional information regarding the use of BEKEMV, you can refer to the Patient Information Leaflet (PIL), or contact Medical Information by e-mail at: medinfo-mea@amgen.com

This document is approved by the Executive Directorate of Pharmacovigilance at SFDA