BEKEMV® ▼(eculizumab)

Physician's Guide

Important information for healthcare providers about serious adverse events or reactions with BEKEMV®

▼ This medicinal product is subject to additional monitoring. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events can also be reported to Amgen Limited on +44 (0) 1223 436441.

AMGEN

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

IMPORTANT INFORMATION

Vaccination/Antibiotic prophylaxis Certificate

In order to minimise the risk of inappropriate use of BEKEMV (eculizumab), the decision of the Medicines and Healthcare products Regulatory Agency (MHRA) requires that drug distribution by Amgen will only be possible after written confirmation that the patient has effectively received meningococcal vaccination and/or antibiotic prophylaxis.

Contact Amgen Medical Information by email at gbinfoline@amgen.com or telephone 01223 436441.

Amgen will not be able to process any orders for patients for which we have not received the Vaccination/Antibiotic prophylaxis Certificate.

BEKEMV [1]

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 the opsonisation of microorganisms, initiation of immune response (both humoral and cellular) and clearance of immune complexes, are preserved.

BEKEMV INDICATIONS [1]

BEKEMV 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 uraemic syndrome (aHUS).

IMPORTANT SAFETY INFORMATION[1]

BEKEMV is contraindicated in babies and young children below 2 years of age, 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.

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 BEKEMV unless the risk of delaying BEKEMV therapy outweighs the risks 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.
- 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.
- In children for whom there is no vaccine recommended or available for use, in patients for whom the vaccine is contra-indicated and in patients treated with BEKEMV less than 2 weeks after receiving a meningococcal vaccine, treat with antibiotic prophylaxis throughout the treatment period or until 2 weeks after the vaccination.
- Revaccinate according to current national vaccination guidelines for vaccine use in patients treated with complement inhibitors.

***Haemophilus influenzae* and pneumococcal infections in children: Vaccination**

- **Patients receiving BEKEMV:** Vaccinate patients less than 18 years against ***Haemophilus influenzae*** and pneumococcal infections according to national vaccination guidelines at least 2 weeks prior to initiation of BEKEMV therapy and strictly adhere to the national vaccination recommendations for each age group.

Impact of vaccination on underlying disease

Vaccination or revaccination may further activate complement and, 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) or thrombotic microangiopathy (TMA), (aHUS). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

SIGNS AND SYMPTOMS OF SEVERE INFECTION

Meningococcal infection

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

- Headache with nausea or vomiting
- Headache and a fever
- Headache with a stiff neck or 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 crying or moaning
- Stiff neck, dislike bright lights
- Refusing food and vomiting
- Drowsy, floppy, unresponsive
- Pale, blotchy skin spots/rash
- Convulsions/seizures

In children, additional signs and symptoms to those listed for infants may include:

- Severe muscle pain
- Sever headache
- Confusion
- Irritability

- **Provide a Patient Safety Card** to patients being treated with **BEKEMV** 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.**
- Physicians 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. Therefore it is important parents/legal guardians are made aware of other symptoms including inactivity, irritability, , vomiting, and food refusal and to seek urgent medical attention.

Other systemic infections

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[1]

Infusion reactions including anaphylaxis

As with all therapeutic proteins, administration of BEKEMV (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 BEKEMV, 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 adults and four hours in paediatric patients aged less than 18 years.

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

This medicine contains 50 mg sorbitol (E420) in each mL and it is given intravenously. BEKEMV is contraindicated in babies and young children (below 2 years of age) who may not yet be diagnosed with Hereditary fructose intolerance (HFI).

Patients with HFI must not be given this medicine unless strictly necessary.

After intravenous administration of a sorbitol-containing medicine like BEKEMV, patients with HFI may present with hypoglycaemia, metabolic acidosis, seizures and coma which could be life threatening[3].

A family history of HFI, and a detailed history of the patient's dietary habits with regard to HFI symptoms must be obtained before starting treatment with BEKEMV.

RISKS ASSOCIATED WITH DISCONTINUATION OF BEKEMV[1]

Serious intravascular haemolysis in patients treated for PNH

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

However, patients who discontinue treatment with BEKEMV 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 lactate dehydrogenase (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 reinstitution of BEKEMV.

Thrombotic microangiopathy in patients treated for aHUS

Patients who start eculizumab as treatment for aHUS should continue receiving eculizumab, even if their condition appears to have improved. Thrombotic microangiopathy (TMA) complications have been observed as early as 4 weeks and up to 127 weeks following discontinuation of eculizumab treatment in some aHUS patients. Discontinuation of treatment should only be considered if medically justified.

If aHUS patients discontinue treatment with BEKEMV, they should be monitored closely for signs and symptoms of severe TMA complications. Monitoring may be insufficient to predict or prevent severe TMA complications in patients with aHUS after discontinuation of BEKEMV.

Severe TMA complications post discontinuation can be identified by (i) 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 (ii) any one of the following: a change in mental status or seizures; angina or dyspnoea; or thrombosis.

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

HOME HEALTHCARE SERVICE

There is a Homecare Infusion Service which is available to patients prescribed BEKEMV who have tolerated infusions well in the clinic. The decision of a patient to receive home infusions should be made after evaluation and recommendation from the treating physician.

For more details on the Homecare Infusion Service, please contact Amgen by email to patientservicesuk@amgen.com or telephone 01223 436441.

REFERENCES

1. BEKEMV® (eculizumab) Summary of Product Characteristics
2. Meningitis: https://www.gov.uk/government/publications/meningococcal-disease-guidance-on-public-health-management
3. Hereditary Fructose Intolerance: https://www.ncbi.nlm.nih.gov/books/NBK333439/

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.

Please report any suspected adverse reactions to www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Reports can also be made to Amgen directly by contacting Medical Information by email to gbinfoline@amgen.com or telephone 01223 436441.

COMPANY CONTACT POINT

Should you have any questions or require additional information regarding the use of BEKEMV, please contact Amgen Medical Information by email to gbinfoline@amgen.com or telephone 01223 436441.