ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

BEKEMV 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eculizumab is a humanised monoclonal ($IgG_{2/4\kappa}$) antibody produced in CHO cell line by recombinant DNA technology.

One vial of 30 mL contains 300 mg of eculizumab (10 mg/mL).

Excipients with known effect

Each mL of solution contains 50 mg sorbitol. Each vial contains 1 500 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear to opalescent, colourless to slightly yellow, pH 5.2 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 5.1).

4.2 Posology and method of administration

BEKEMV must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological disorders.

Home infusion may be considered for patients 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. Home infusions should be performed by a qualified healthcare professional.

Posology

PNH in adults

The PNH dosing regimen for adult patients (≥ 18 years of age) consists of a 4-week initial phase followed by a maintenance phase:

- Initial phase: 600 mg of BEKEMV administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.

- Maintenance phase: 900 mg of BEKEMV administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 900 mg of BEKEMV administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days (see section 5.1).

Paediatric patients in PNH

Paediatric PNH patients with body weight ≥ 40 kg are treated with the adult dosing recommendations.

BEKEMV is contraindicated in children below 2 years of age (see section 4.3).

In paediatric PNH patients above 2 years of age and with body weight below 40 kg, the BEKEMV dosing regimen consists of:

Patient body weight	**Initial phase**	**Maintenance phase**
30 to < 40 kg	600 mg weekly for the first 2 weeks	900 mg at week 3; then 900 mg every 2 weeks
20 to < 30 kg	600 mg weekly for the first 2 weeks	600 mg at week 3; then 600 mg every 2 weeks
10 to < 20 kg	600 mg single dose at week 1	300 mg at week 2; then 300 mg every 2 weeks
5 to < 10 kg	300 mg single dose at week 1	300 mg at week 2; then 300 mg every 3 weeks

Eculizumab has not been studied in patients with PNH who weigh less than 40 kg.

Duration of use

BEKEMV treatment is recommended to continue for the patient's lifetime, unless the discontinuation of BEKEMV is clinically indicated (see section 4.4).

Special populations

Elderly
BEKEMV may be administered to patients aged 65 years and over. There is no evidence to suggest that any special precautions are needed when older people are treated – although experience with eculizumab in this patient population is still limited.

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

Hepatic impairment
The safety and efficacy of BEKEMV have not been studied in patients with hepatic impairment (see section 5.2).

Method of administration

BEKEMV should not be administered as an intravenous push or bolus injection. BEKEMV should only be administered via intravenous infusion as described below.

For instructions on dilution of the medicinal product before administration, see section 6.6.

The diluted solution of BEKEMV should be administered by intravenous infusion over 25 - 45 minutes (35 minutes ± 10 minutes) in adults and 1 - 4 hours in paediatric patients under 18 years of age via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of BEKEMV from light during administration to the patient.

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 under 18 years of age.

There is limited safety data supporting home-based infusions, additional precautions in the home setting such as availability of emergency treatment of infusion reactions or anaphylaxis are recommended.

Infusion reactions are described in sections 4.4 and 4.8.

4.3 Contraindications

Hypersensitivity to eculizumab or to any of the excipients listed in section 6.1.

BEKEMV is contraindicated in subjects with hereditary fructose intolerance (HFI). Prior to initiating treatment HFI should be excluded on age-appropriate clinical grounds (see section 4.4).

BEKEMV is contraindicated in babies and children below 2 years of age since they may not yet be diagnosed with hereditary fructose intolerance (HFI) (see section 4.4).

BEKEMV therapy must not be initiated in patients (see section 4.4):
- with unresolved *Neisseria meningitidis* infection
- who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

4.4 Special warnings and precautions for use

BEKEMV is not expected to affect the aplastic component of anaemia in patients with PNH.

Meningococcal infection

Due to its mechanism of action, the use of BEKEMV increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving BEKEMV unless the risk of delaying BEKEMV therapy outweighs the risks of developing a meningococcal infection. Patients who initiate BEKEMV treatment less than 2 weeks after receiving a tetravalent meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, and W 135, are recommended in preventing the commonly pathogenic meningococcal serogroups. Vaccine against serogroup B where available is also recommended. Patients must receive vaccination according to current national vaccination guidelines for vaccination use.

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

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. 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 (see section 4.8). 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 should be informed of these signs and symptoms and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of BEKEMV therapy with patients and provide them with a patient information brochure and a patient safety card (see package leaflet for a description).

Other systemic infections

Due to its mechanism of action, BEKEMV therapy should be administered with caution to patients with active systemic infections. Patients may have increased susceptibility to infections, especially with *Neisseria* and encapsulated bacteria. Serious infections with *Neisseria species* (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported. Patients should be provided with information from the package leaflet to increase their awareness of potential serious infections and the signs and symptoms of them. Physicians should advise patients about gonorrhoea prevention.

Infusion reactions

Administration of BEKEMV may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials, 1 (0.9%) refractory generalised myasthenia gravis (gMG) patient experienced an infusion reaction which required discontinuation of eculizumab. No PNH patients experienced an infusion reaction which required discontinuation of eculizumab. BEKEMV administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered.

Immunogenicity

Anti-eculizumab antibodies may develop during eculizumab treatment. No apparent correlation of antibody development with clinical response or adverse events has been observed.

Immunisation

Prior to initiating BEKEMV therapy, it is recommended that PNH patients initiate immunisations according to current immunisation guidelines. Additionally, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to receiving BEKEMV unless the risk of delaying BEKEMV therapy outweighs the risks of developing a meningococcal infection. Patients who initiate BEKEMV treatment less than 2 weeks after receiving a tetravalent meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y and W 135 are recommended in preventing the commonly pathogenic meningococcal serogroups. Vaccine against serogroup B where available is also recommended (see meningococcal infection).

Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations for each age group.

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

Anticoagulant therapy

Treatment with BEKEMV should not alter anticoagulant management.

PNH laboratory monitoring

PNH patients should be monitored for signs and symptoms of intravascular haemolysis, including serum lactate dehydrogenase (LDH) levels. PNH patients receiving BEKEMV therapy should be similarly monitored for intravascular haemolysis by measuring LDH levels and may require dose adjustment within the recommended 14 ± 2 day dosing schedule during the maintenance phase (up to every 12 days).

Treatment discontinuation for PNH

If PNH patients discontinue treatment with BEKEMV they should be closely monitored for signs and symptoms of serious intravascular haemolysis. Serious haemolysis is identified by serum LDH levels greater than the pre-treatment level, along with any of the following: 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. Monitor any patient who discontinues BEKEMV for at least 8 weeks to detect serious haemolysis and other reactions.

If serious haemolysis occurs after BEKEMV discontinuation, consider the following procedures/treatments: blood transfusion (packed red blood cells or RBCs), or exchange transfusion if the PNH RBCs are > 50% of the total RBCs by flow cytometry; anticoagulation; corticosteroids; or reinstitution of BEKEMV. In PNH clinical studies, 16 patients discontinued the eculizumab treatment regimen. Serious haemolysis was not observed.

Educational materials

All physicians who intend to prescribe BEKEMV must ensure they are familiar with the physician's guide to prescribing. Physicians must discuss the benefits and risks of BEKEMV therapy with patients and provide them with a patient information brochure and a patient safety card.

Patients should be instructed that if they develop fever, headache accompanied with fever and/or stiff neck or sensitivity to light, they should immediately seek medical care as these signs may be indicative of meningococcal infection.

Excipients with known effect

Sorbitol

Each mL of this medicinal product contains 50 mg of sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not take this medicine. In HFI patients more than 2 years old, a spontaneous aversion for fructose-containing foods develops and may be combined with the onset of symptoms (vomiting, gastro-intestinal disorders, apathy, height and weight retardation). Therefore, a detailed history with regards to HFI symptoms has to be taken of each patient prior to receiving BEKEMV. In case of inadvertent administration and suspicion of 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 (see section 4.3).

Babies and children (below 2 years of age) may not yet be diagnosed with HFI. Medicines containing sorbitol/fructose given intravenously may be life threatening and must be contraindicated in this population (see sections 4.2 and 4.3).

Sodium

BEKEMV vials contain less than 1 mmol of sodium (23 mg) per dose, that is to say essentially "sodium free". On dilution with 5% glucose solution, the medicinal product is essentially "sodium free".

Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicinal product contains 0.34 g sodium per 180 mL at the maximal dose, equivalent to 17.0% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Once diluted with sodium chloride 4.5 mg/mL (0.45%) solution for injection, this medicinal product contains 0.18 g sodium per 180 mL at the maximal dose, equivalent to 9.0% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on the potential inhibitory effect of eculizumab on complement-dependent cytotoxicity of rituximab, eculizumab may reduce the expected pharmacodynamic effects of rituximab.

Concomitant use of eculizumab with intravenous immunoglobulin (IVIg) may reduce effectiveness of eculizumab. Closely monitor for reduced effectiveness of eculizumab.

Concomitant use of eculizumab with neonatal Fc receptor (FcRn) blockers may lower systemic exposures and reduce effectiveness of eculizumab. Closely monitor for reduced effectiveness of eculizumab.

4.6 Fertility, pregnancy and lactation

The use of adequate contraception to prevent pregnancy and for at least 5 months after the last dose of treatment with eculizumab should be considered for women of childbearing potential.

Pregnancy

There are no well-controlled studies in pregnant women treated with eculizumab. Data on a limited number of pregnancies exposed to eculizumab (less than 300 pregnancy outcomes) indicate there is no increased risk of foetal malformation or foetal-neonatal toxicity. However, due to the lack of well-controlled studies, uncertainties remain. Therefore, an individual benefits and risk analysis is recommended before starting and during treatment with eculizumab in pregnant women. Should such a treatment be considered necessary during pregnancy, a close maternal and foetal monitoring according to local guidelines is recommended.

Animal reproduction studies have not been conducted with eculizumab (see section 5.3).

Human IgG are known to cross the human placental barrier, and thus eculizumab may potentially cause terminal complement inhibition in the foetal circulation. Therefore, BEKEMV should be given to a pregnant woman only if clearly needed.

Breast-feeding

No effects on the breastfed new-born/infant are anticipated as limited data available suggest that eculizumab is not excreted in human breast milk. However, due to the limitations of the available data, the developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for eculizumab and any potential adverse effects on the breastfed child from eculizumab or from the underlying maternal condition.

Fertility

No specific study of eculizumab on fertility has been conducted.

4.7 Effects on ability to drive and use machines

BEKEMV has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Supportive safety data were obtained from 33 clinical studies that included 1 555 patients exposed to eculizumab in complement-mediated disease populations, including PNH, aHUS, refractory generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD). The most common adverse reaction was headache, (occurred mostly in the initial phase of dosing), and the most serious adverse reaction was meningococcal infection.

Tabulated list of adverse reactions

Table 1 gives the adverse reactions observed from spontaneous reporting and in eculizumab completed clinical trials, including PNH, aHUS, refractory gMG and NMOSD studies. Adverse reactions reported at a very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) or rare (≥ 1/10 000 to < 1/1 000) frequency with eculizumab, are listed by system organ class and preferred term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in eculizumab clinical trials, including patients with PNH, aHUS, refractory gMG and NMOSD as well as from post marketing experience

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**
Infections and infestations		Pneumonia, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Urinary tract infection, Oral herpes	Meningococcal infection[b], Sepsis, Septic shock, Peritonitis, Lower respiratory tract infection, Fungal infection, Viral infection, Abscess[a], Cellulitis, Influenza, Gastrointestinal infection, Cystitis, Infection, Sinusitis, Gingivitis	Aspergillus infection[c], Arthritis bacterial[c], Genitourinary tract gonococcal infection, *Haemophilus influenzae* infection, Impetigo

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Malignant melanoma, Myelodysplastic syndrome
Blood and lymphatic system disorders		Leucopenia, Anaemia	Thrombocytopenia, Lymphopenia	Haemolysis*, Abnormal clotting factor, Red blood cell agglutination, Coagulopathy
Immune system disorders			Anaphylactic reaction, Hypersensitivity	
Endocrine disorders				Basedow's disease
Metabolism and nutrition disorders			Decreased appetite	
Psychiatric disorders		Insomnia	Depression, Anxiety, Mood swings, Sleep disorder	Abnormal dreams
Nervous system disorders	Headache	Dizziness	Paraesthesia, Tremour, Dysgeusia, Syncope	
Eye disorders			Vision blurred	Conjunctival irritation
Ear and labyrinth disorders			Tinnitus, Vertigo	
Cardiac disorders			Palpitation	
Vascular disorders		Hypertension	Accelerated hypertension, Hypotension, Hot flush, Vein disorder	Haematoma
Respiratory, thoracic and mediastinal disorders		Cough, Oropharyngeal pain	Dyspnoea, Epistaxis, Throat irritation, Nasal congestion, Rhinorrhoea	
Gastrointestinal disorders		Diarrhoea, Vomiting, Nausea, Abdominal pain	Constipation, Dyspepsia, Abdominal distension	Gastroesophageal reflux disease, Gingival pain
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia	Urticaria, Erythema, Petechiae, Hyperhidrosis, Dry skin, Dermatitis	Skin depigmentation
Musculoskeletal and connective tissue disorders		Arthralgia, Myalgia, Pain in extremity	Muscle spasms, Bone pain, Back pain, Neck pain	Trismus, Joint swelling
Renal and urinary disorders			Renal impairment, Dysuria, Haematuria	
Reproductive system and breast disorders			Spontaneous penile erection	Menstrual disorder

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to < 1/1 000)
General disorders and administration site conditions		Pyrexia, Fatigue, Influenza like illness	Oedema, Chest discomfort, Asthaenia, Chest pain, Infusion site pain, Chills	Extravasation, Infusion site paraesthesia, Feeling hot
Investigations			Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased	Coombs test positive[c]
Injury, poisoning and procedural complications		Infusion related reaction		

Included studies: asthma (C07-002), aHUS (C08-002, C08-003, C10-003, C10-004), dermatomyositis (C99-006), refractory gMG (C08-001, ECU-MG-301, ECU-MG-302, ECU-MG-303), Neuromyelitis Optica Spectrum Disorder (ECU-NMO-301, ECU-NMO-302), IMG (C99-004, E99-004), PNH (C02-001, C04-001, C04-002, C06-002, C07-001, E02-001, E05-001, E07-001, M07-005,
X03-001, X03-001A), psoriasis (C99-007), RA (C01-004, C97-001, C99-001, E01-004, E99-001), STEC-HUS (C11-001), SLE (C97-002). MedDRA version 24.1.

* See 'Description of selected adverse reactions.'

[a] Abscess includes the following group of preferred terms (PTs): abscess limb, colonic abscess, renal abscess, subcutaneous abscess, tooth abscess, hepatosplenic abscess, perirectal abscess, rectal abscess.

[b] Meningococcal infection includes the following group of PTs: meningococcal infection, meningococcal sepsis, meningitis meningococcal, *Neisseria* infection.

[c] ADRs identified in post marketing reports.

Description of selected adverse reactions

In all clinical studies, the most serious adverse reaction was meningococcal sepsis which is a common presentation of meningococcal infections in patients treated with eculizumab (see section 4.4). Other cases of *Neisseria species* have been reported including sepsis with *Neisseria gonorrhoeae*, *Neisseria sicca/subflava*, *Neisseria spp* unspecified.

Antibodies to eculizumab were detected in patients with PNH. As with all proteins there is a potential for immunogenicity.

Cases of haemolysis have been reported in the setting of missed or delayed eculizumab dose in PNH clinical trials (see section 4.4).

Cases of thrombotic microangiopathy complication have been reported in the setting of missed or delayed eculizumab dose in aHUS clinical trials.

Paediatric population

In children and adolescent PNH patients (aged 11 years to less than 18 years) included in the paediatric PNH study M07-005, the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reaction reported in paediatric patients was headache.

Other special population

Elderly population

No overall differences in safety were reported between elderly (≥ 65 years) and younger refractory gMG patients (< 65 years) (see section 5.1).

Patients with other diseases

Safety data from other clinical studies
Supportive safety data were obtained in 12 completed clinical studies that included 934 patients exposed to eculizumab in other disease populations other than PNH, aHUS, refractory gMG or NMOSD. There was an un-vaccinated patient diagnosed with idiopathic membranous glomerulonephropathy who experienced meningococcal meningitis. Adverse reactions reported in patients with disease other than PNH, aHUS, refractory gMG or NMOSD were similar to those reported in patients with PNH, aHUS, refractory gMG or NMOSD (see table 1 above). No specific adverse reactions have emerged from these clinical studies.

Reporting of suspected adverse 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 via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported in any of the clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AJ01

BEKEMV is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency; www.ema.europa.eu.

BEKEMV is a recombinant humanised monoclonal $IgG_{2/4k}$ antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement. The BEKEMV antibody contains human constant regions and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. BEKEMV is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

BEKEMV is produced in a CHO cell line and purified by affinity and ion exchange chromatography. The bulk active substance manufacturing process also includes specific viral inactivation and removal steps.

Mechanism of action

Eculizumab, the active substance in BEKEMV, is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

In PNH patients, uncontrolled terminal complement activation and the resulting complement-mediated intravascular haemolysis are blocked with BEKEMV treatment.

In most PNH patients, eculizumab serum concentrations of approximately 35 micrograms/mL are sufficient for essentially complete inhibition of terminal complement-mediated intravascular haemolysis.

In PNH, chronic administration of BEKEMV resulted in a rapid and sustained reduction in complement-mediated haemolytic activity.

Clinical efficacy and safety

Paroxysmal nocturnal haemoglobinuria

The safety and efficacy of eculizumab in PNH patients with haemolysis were assessed in a randomised, double-blind, placebo-controlled 26 week study (C04-001). PNH patients were also treated with eculizumab in a single arm 52 week study (C04-002), and in a long-term extension study (E05-001). Patients received meningococcal vaccination prior to receipt of eculizumab. In all studies, the dose of eculizumab was 600 mg every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Eculizumab was administered as an intravenous infusion over 25 – 45 minutes (35 minutes ± 10 minutes). An observational non-interventional registry in patients with PNH (M07-001) was also initiated to characterise the natural history of PNH in untreated patients and the clinical outcomes during eculizumab treatment.
In study C04-001 (TRIUMPH) PNH patients with at least 4 transfusions in the prior 12 months flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100 000/microlitre were randomised to either eculizumab (n = 43) or placebo (n = 44). Prior to randomisation, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the haemoglobin concentration (the "set-point") which would define each patient's haemoglobin stabilisation and transfusion outcomes. The haemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Primary efficacy endpoints were haemoglobin stabilisation (patients who maintained a haemoglobin concentration above the haemoglobin set-point and avoid any RBC transfusion for the entire 26 week period) and blood transfusion requirement. Fatigue and health-related quality of life were relevant secondary endpoints.

Haemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medicinal products. Major baseline characteristics were balanced (see table 2).

In the non-controlled study C04-002 (SHEPHERD), PNH patients with at least one transfusion in the prior 24 months and at least 30 000 platelets/microlitre received eculizumab over a 52-week period. Concomitant medicinal products included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Baseline characteristics are shown in table 2.

Table 2. Patient demographics and characteristics in C04-001 and C04-002

	C04-001		**C04-002**
Parameter	**Placebo** N = 44	**Eculizumab** N = 43	**Eculizumab** N = 97
Mean age (SD)	38.4 (13.4)	42.1 (15.5)	41.1 (14.4)
Gender - female (%)	29 (65.9)	23 (53.5)	49 (50.5)
History of aplastic anaemia or MDS (%)	12 (27.3)	8 (18.7)	29 (29.9)
Concomitant anticoagulants (%)	20 (45.5)	24 (55.8)	59 (61)

	C04-001		C04-002
Parameter	**Placebo** N = 44	**Eculizumab** N = 43	**Eculizumab** N = 97
Concomitant steroids/immunosuppressant treatments (%)	16 (36.4)	14 (32.6)	46 (47.4)
Discontinued treatment	10	2	1
PRBC in previous 12 months (median (Q1, Q3))	17.0 (13.5, 25.0)	18.0 (12.0, 24.0)	8.0 (4.0, 24.0)
Mean Hgb level (g/dL) at setpoint (SD)	7.7 (0.75)	7.8 (0.79)	N/A
Pre-treatment LDH levels (median, U/L)	2 234.5	2 032.0	2 051.0
Free haemoglobin at baseline (median, mg/dL)	46.2	40.5	34.9

In TRIUMPH, study patients treated with eculizumab had significantly reduced ($p < 0.001$) haemolysis resulting in improvements in anaemia as indicated by increased haemoglobin stabilisation and reduced need for RBC transfusions compared to placebo treated patients (see table 3). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; > 25 units). After 3 weeks of eculizumab treatment, patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of eculizumab on thrombotic events could not be determined. In SHEPHERD study, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular haemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in increased transfusion avoidance, a reduced need for RBC transfusion and less fatigue (see table 3).

Table 3. Efficacy outcomes in C04-001 and C04-002

	C04-001			C04-002*	
	Placebo N = 44	**Eculizumab** N = 43	**P – value**	**Eculizumab** N = 97	**P – value**
Percentage of patients with stabilised haemoglobin levels at end of study	0	49	< 0.001	N/A	
PRBC transfused during treatment (median)	10	0	< 0.001	0	< 0.001
Transfusion avoidance during treatment (%)	0	51	< 0.001	51	< 0.001
LDH levels at end of study (median, U/L)	2 167	239	< 0.001	269	< 0.001
LDH AUC at end of study (median, U/L × Day)	411 822	58 587	< 0.001	-632 264	< 0.001
Free haemoglobin at end of study (median, mg/dL)	62	5	< 0.001	5	< 0.001
FACIT-fatigue (effect size)		1.12	< 0.001	1.14	< 0.001

* Results from study C04-002 refer to pre- versus post-treatment comparisons.

From the 195 patients that originated in C04-001, C04-002 and other initial studies, eculizumab - treated PNH patients were enrolled in a long-term extension study (E05-001). All patients sustained a reduction in intravascular haemolysis over a total eculizumab exposure time ranging from 10 to 54 months. There were fewer thrombotic events with eculizumab treatment than during the same period of time prior to treatment. However, this finding was shown in non-controlled clinical trials.

The PNH registry (M07-001) was used to evaluate the efficacy of eculizumab in PNH patients with no history of RBC transfusion. These patients had high disease activity as defined by elevated haemolysis (LDH ≥ 1.5 × ULN) and the presence of related clinical symptom(s): fatigue, haemoglobinuria,

abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 100 g/L), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction.

In the PNH registry, patients treated with eculizumab were observed to have a reduction in haemolysis and associated symptoms. At 6 months, patients treated with eculizumab with no history of RBC transfusion had significantly ($p < 0.001$) reduced LDH levels (median LDH of 305 U/L; see table 4). Furthermore, 74% of the patients without a history of transfusion and treated with eculizumab experienced clinically meaningful improvements in FACIT-fatigue score (i.e., increase by 4 points or more) and 84% in EORTC fatigue score (i.e., decrease by 10 points or more).

Table 4. Efficacy outcomes (LDH level and FACIT-fatigue) in patients with PNH with no history of transfusion in M07-001

	M07-001
Parameter	**Eculizumab No transfusion**
LDH level at baseline (median, U/L)	N = 43 1 447
LDH level at 6 months (median, U/L)	N = 36 305
FACIT-fatigue score at baseline (median)	N = 25 32
FACIT-fatigue score at last available assessment (median)	N = 31 44

FACIT-fatigue is measured on a scale of 0 - 52, with higher values indicating less fatigue

Paediatric population

Paroxysmal nocturnal haemoglobinuria

A total of 7 PNH paediatric patients, with a median weight of 57.2 kg (range of 48.6 to 69.8 kg) and aged from 11 to 17 years (median age: 15.6 years), received eculizumab in study M07-005.

Treatment with eculizumab at the proposed dosing regimen in the paediatric population was associated with a reduction of intravascular haemolysis as measured by serum LDH level. It also resulted in a marked decrease or elimination of blood transfusions, and a trend towards an overall improvement in general function. The efficacy of eculizumab treatment in paediatric PNH patients appears to be consistent with that observed in adult PNH patients enrolled in PNH pivotal studies (C04-001 and C04-002) (see tables 3 and 5).

Table 5. Efficacy outcomes in paediatric PNH study M07-005

		P – Value	
	Mean (SD)	**Wilcoxon signed rank**	**Paired t-test**
Change from baseline at 12 weeks of LDH value (U/L)	-771 (914)	0.0156	0.0336
LDH AUC (U/L × day)	-60 634 (72 916)	0.0156	0.0350
Change from baseline at 12 weeks in plasma free haemoglobin (mg/dL)	-10.3 (21.13)	0.2188	0.1232
Change from baseline type III RBC clone size (percent of aberrant cells)	1.80 (358.1)		
Change from baseline at 12 weeks of PedsQL™ 4.0 generic core scale (patients)	10.5 (6.66)	0.1250	0.0256
Change from baseline at 12 weeks of PedsQL™ 4.0 generic core scale (parents)	11.3 (8.5)	0.2500	0.0737

		P – Value	
	Mean (SD)	**Wilcoxon signed rank**	**Paired t-test**
Change from baseline at 12 weeks of PedsQL™ multidimensional fatigue (patients)	0.8 (21.39)	0.6250	0.4687
Change from baseline at 12 weeks of PedsQL™ multidimensional fatigue (parents)	5.5 (0.71)	0.5000	0.0289

5.2 Pharmacokinetic properties

Pharmacokinetics and active substance metabolism

Biotransformation

Human antibodies undergo endocytotic digestion in the cells of the reticuloendothelial system. Eculizumab contains only naturally occurring amino acids and has no known active metabolites. Human antibodies are predominately catabolised by lysosomal enzymes to small peptides and amino acids.

Elimination

No specific studies have been performed to evaluate the hepatic, renal, lung, or gastrointestinal routes of excretion/elimination for eculizumab. In normal kidneys, antibodies are not excreted and are excluded from filtration by their size.

Pharmacokinetic/pharmacodynamic relationship(s)

In 40 patients with PNH, a 1-compartmental model was used to estimate pharmacokinetic parameters after multiple doses. Mean clearance was 0.31 ± 0.12 mL/hr/kg, mean volume of distribution was 110.3 ± 17.9 mL/kg, and mean elimination half-life was 11.3 ± 3.4 days. The steady state is achieved by 4 weeks using the PNH adult dosing regimen.

In PNH patients, pharmacodynamic activity correlates directly with eculizumab serum concentrations and maintenance of trough levels above ≥ 35 micrograms/mL results in essentially complete blockade of haemolytic activity in the majority of PNH patients.

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange resulted in an approximately 50% decline in eculizumab concentrations following a 1-hour intervention and the elimination half-life of eculizumab was reduced to 1.3 hours.

Pharmacodynamic activity measured by free C5 concentrations of < 0.5 micrograms/mL, is correlated with essentially complete blockade of terminal complement activity in PNH patients.

Special Populations

Dedicated studies have not been conducted to evaluate the pharmacokinetics of eculizumab in special patient populations identified by gender, race, age (geriatric), or the presence of renal or hepatic impairment.

Population PK analysis on data collected across eculizumab studies showed that gender, race, age (geriatric), or the presence of renal or hepatic impairment function do not influence the PK of eculizumab. Body weight was a significant covariate resulting in a lower eculizumab clearance in paediatric patients requiring body weight-based dosing in paediatric patients.

Paediatric population

The pharmacokinetics of eculizumab in PNH paediatric patients (aged from 11 to less than 18 years) with body-weight-based dose regimen was evaluated in study M07-005.

Weight was a significant covariate resulting in a lower eculizumab clearance 0.0105 L/h in the adolescent PNH patients.

5.3 Preclinical safety data

The specificity of eculizumab for C5 in human serum was evaluated in two *in vitro* studies.

The tissue cross-reactivity of eculizumab was evaluated by assessing binding to a panel of 38 human tissues. C5 expression in the human tissue panel examined in this study is consistent with published reports of C5 expression, as C5 has been reported in smooth muscle, striated muscle, and renal proximal tubular epithelium. No unexpected tissue cross-reactivity was observed.

Animal reproduction studies have not been conducted with eculizumab due to lack of pharmacologic activity in non-human species.

In a 26 week toxicity study performed in mice with a surrogate antibody directed against murine C5, treatment did not affect any of the toxicity parameters examined. Haemolytic activity during the course of the study was effectively blocked in both female and male mice.

No clear treatment-related effects or adverse effects were observed in reproductive toxicology studies in mice with a surrogate terminal complement inhibitory antibody, which was utilised to assess the reproductive safety of C5 blockade. These studies included assessment of fertility and early embryonic development, developmental toxicity, and pre- and post-natal development.

When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose (approximately 4 times the maximum recommended human eculizumab dose, based on a body weight comparison); however, the exposure did not increase foetal loss or neonatal death.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of eculizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Sodium hydroxide
Disodium edetate (EDTA)
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After dilution, chemical and physical in-use stability has been demonstrated for the following:

- Polyolefin IV bags: 14 days at 2°C to 8°C followed by up to 48 hours at 2°C to 8°C or room temperature
- PVC IV bags: 48 hours at 2°C to 8°C or room temperature

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.

BEKEMV vials in the original package may be removed from refrigerated storage for only one single period of up to 7 days. At the end of this period the product can be put back in the refrigerator.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (type I glass) with an elastomeric stopper and an aluminium seal with flip-off cap.
Pack size of one vial.

6.6 Special precautions for disposal and other handling

Prior to administration, the BEKEMV solution should be visually inspected for particulate matter and discolouration.

Instructions

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

Withdraw the total amount of BEKEMV from the vial(s) using a sterile syringe.

Transfer the recommended dose to an infusion bag.

Dilute BEKEMV to a final concentration of 5 mg/mL by addition to the infusion bag using sodium chloride 9 mg/mL (0.9%) solution for injection, sodium chloride 4.5 mg/mL (0.45%) solution for injection, or 5% glucose in water, as the diluent.

The final volume of a 5 mg/mL diluted solution is 60 mL for 300 mg doses, 120 mL for 600 mg doses and 180 mL for 900 mg doses. The solution should be clear and colourless.

Gently agitate the infusion bag containing the diluted solution to ensure thorough mixing of the product and diluent.

The diluted solution should be allowed to warm to room temperature prior to administration by exposure to ambient temperature.

Discard any unused portion left in a vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Amgen Technology (Ireland) UC
Pottery Road, Dun Laoghaire
Co. Dublin,
A96 F2A8 Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1727/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Amgen Singapore Manufacturing
1 Tuas View Drive
Singapore 637026

Name and address of the manufacturers responsible for batch release

Amgen Technology (Ireland) UC
Pottery Road, Dun Laoghaire
Co. Dublin,
A96 F2A8 Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall agree the details of a controlled drug distribution system and educational material including a patient safety card with each national competent authority and must implement such programmes nationally to ensure that:

1. All healthcare professionals who may prescribe eculizumab receive the appropriate educational material.
2. All patients being treated with eculizumab receive a patient safety card.
3. Drug distribution will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis.
4. Vaccination reminders are sent to the prescribers.

The educational material should be agreed with the National Competent Authority and should contain the following:

- Summary of product characteristics
- Physician's guide to prescribing
- Package leaflet
- Patient's/parent's information brochures
- Patient safety card

The physician's guides to prescribing should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- All patients must be monitored for signs of meningococcal infection.
- The need for patients to be vaccinated against *Neisseria meningitidis* two weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis.
- The requirement to vaccinate children against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- There is an important risk of Aspergillus infection in patients treated with eculizumab. The healthcare professionals should be advised to look for risk factors and signs and symptoms of Aspergillus infection. Practical advice should be included to mitigate the risk.
- The risk of infusion reactions including anaphylaxis and advice on post-infusion monitoring.
- The risk of developing antibodies to eculizumab.
- Risk of serious haemolysis following eculizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
- Sorbitol content warning and the risks for patients with HFI when intravenously exposed to sorbitol.
- BEKEMV contraindication in patients with HFI (regardless of their age), and in children below 2 years of age, who may not yet be diagnosed with HFI.
- The need to explain to and ensure understanding of by patients/carers:
    - the risks of treatment with eculizumab
    - the signs and symptoms of sepsis/severe infection and what action to take
    - the patient's/carer's guides and their contents
    - the need to carry the patient safety card and to tell any healthcare professional that he/she is receiving treatment with eculizumab
    - the requirement for vaccinations/antibiotic prophylaxis
    - the risks of serious metabolic harms due to treatment with BEKEMV if the patient also has HFI

The patient's/parent's guides should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection, especially *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- Signs and symptoms of severe infection and the need to obtain urgent medical care.
- The patient safety card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with eculizumab.
- The importance of meningococcal vaccination prior to treatment with eculizumab and/or to receive antibiotic prophylaxis.
- The need for children to be vaccinated against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- The risk of infusion reactions with eculizumab, including anaphylaxis, and the need for clinical monitoring post-infusion.
- Risk of serious haemolysis (in PNH) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations
- The risks of serious metabolic harms (potentially life-threatening) due to treatment with BEKEMV if the patient also has HFI.
- BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI.

The patient safety card should contain:

- Signs and symptoms of infection and sepsis.
- Warning to seek immediate medical care if above are present.
- Statement that the patient is receiving eculizumab.
- Sorbitol content warning and potentially life-threatening risks of patients with HFI who are intravenously exposed to sorbitol-containing medicines.
- BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI.
- Contact details where a health care professional can receive further information.

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense BEKEMV, a reminder in order that the prescriber/pharmacist checks if a (re)-vaccination against *Neisseria meningitidis* is needed for his/her patients on BEKEMV.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

BEKEMV 300 mg concentrate for solution for infusion
eculizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 30 mL contains 300 mg of eculizumab (10 mg/mL).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, disodium edetate (EDTA), sorbitol, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 30 mL (10 mg/mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
After dilution, the final concentration of the solution to be infused is 5 mg/mL.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Patients with hereditary fructose intolerance (HFI) and children <2 years of age must not be given this medicine due to sorbitol content.
See package leaflet for further information.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC – 8ºC).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Technology (Ireland) UC,
Pottery Road, Dun Laoghaire,
Co. Dublin,
A96 F2A8 Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1727/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

BEKEMV 300 mg concentrate for solution for infusion
eculizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 30 mL contains 300 mg of eculizumab (10 mg/mL).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, disodium edetate (EDTA), sorbitol, polysorbate 80 and water for injections.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 30 mL (10 mg/mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
After dilution, the final concentration of the solution to be infused is 5 mg/mL.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Technology (Ireland) UC,
Pottery Road, Dun Laoghaire,
Co. Dublin,
A96 F2A8 Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1727/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

BEKEMV 300 mg concentrate for solution for infusion
eculizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What BEKEMV is and what it is used for

What is BEKEMV

BEKEMV contains the active substance eculizumab and it belongs to a class of medicines called monoclonal antibodies. Eculizumab binds to and inhibits a specific protein in the body that causes inflammation and so prevents your body's systems from attacking and destroying vulnerable blood cells.

What is BEKEMV used for

Paroxysmal nocturnal haemoglobinuria

BEKEMV is used to treat adults and children with a certain type of disease affecting the blood system called Paroxysmal Nocturnal Haemoglobinuria (PNH). In patients with PNH, their red blood cells can be destroyed which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots. Eculizumab can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable PNH blood cells.

2. What you need to know before you use BEKEMV

Do not use BEKEMV
- If you are allergic to eculizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have fructose intolerance, a quite rare genetic condition where the enzyme for breaking down fructose is not produced.

- Children below 2 years of age must not receive this medicine. This medicine contains sorbitol and sorbitol may be fatal in hereditary fructose intolerance (HFI). In babies and children below 2 years of age HFI may not yet be diagnosed. (See special warnings at the end of this section under subtitle “BEKEMV contains sorbitol”).
- If you have not been vaccinated against meningococcal infection unless you take antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
- If you have a meningococcal infection.

Warnings and precautions

Meningococcal and other Neisseria infections alert

BEKEMV treatment may reduce your natural resistance to infections, especially against certain organisms that cause meningococcal infection (severe infection of the linings of the brain and sepsis) and other *Neisseria* infections including disseminated gonorrhoea.

Consult your doctor before you take BEKEMV to be sure that you receive vaccination against *Neisseria meningitidis*, an organism that causes meningococcal infection, at least 2 weeks before beginning therapy, or that you take antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.

Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

If you are at risk of gonorrhoea, ask your doctor or pharmacist for advice before using this medicine.

Meningococcal infection symptoms

Because of the importance of rapidly identifying and treating certain types of infection in patients who receive BEKEMV, you will be provided a card to carry with you, listing specific trigger symptoms. This card is named: “Patient Safety Card”.

If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache with a stiff neck or back
- fever
- rash
- confusion
- severe muscle aches combined with flu-like symptoms
- sensitivity to light

Treatment for meningococcal infection while travelling

If you are travelling in a remote region where you are unable to contact your doctor or in which you find yourself temporarily unable to receive medical treatment, your doctor can make arrangements to issue, as a preventive measure, a prescription for an antibiotic to counter *Neisseria meningitidis* that you keep with you. If you experience any of the symptoms amongst those cited above, you should take the antibiotics as prescribed. You should bear in mind that you should see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections

Before starting BEKEMV, inform your doctor if you have any infections.

Allergic reactions

BEKEMV contains a protein and proteins can cause allergic reactions in some people.

Children and adolescents

Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Older people

There are no special precautions needed for the treatment of patients aged from 65 years and over.

Other medicines and BEKEMV

Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Women of childbearing potential

The use of effective contraception during treatment and up to 5 months after treatment should be considered in women who are able to get pregnant.

Driving and using machines

BEKEMV has no or negligible influence on the ability to drive and use machines.

BEKEMV contains sorbitol

This medicine contains 50 mg sorbitol in each mL.

Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

Sodium

BEKEMV contains sodium when diluted with sodium chloride.
This medicine contains less than 1 mmol of sodium (23 mg) per dose, that is to say essentially "sodium free".
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicinal product contains 0.34 g sodium (main component of cooking/table salt) per 180 mL at the maximal dose. This is equivalent to 17.0% of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.
Once diluted with sodium chloride 4.5 mg/mL (0.45%) solution for injection, this medicinal product contains 0.18 g sodium (main component of cooking/table salt) per 180 mL at the maximal dose, equivalent to 9.0% of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.

If your health care professional dilutes BEKEMV vials with 5% glucose solution, the medicinal product is essentially “sodium free”.

3. How to use BEKEMV

At least 2 weeks before you start treatment with BEKEMV, your doctor will administer a vaccine against meningococcal infection if it was not previously administered or if your vaccination is outdated. If your child is below the age of vaccination or if you are not vaccinated at least 2 weeks before you start treatment with BEKEMV, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.

Your doctor will administer a vaccine to your child aged less than 18 years against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use

The treatment will be given by your doctor or other health care provider by infusing a dilution of the BEKEMV vial from a drip bag through a tube directly into one of your veins. It is recommended that the beginning of your treatments, called the initial phase, will extend over 4 weeks, followed by a maintenance phase.

<u>If you use this medicine to treat PNH</u>

For adults:
- Initial phase:

Every week for the first four weeks, your doctor will administer an intravenous infusion of diluted BEKEMV**.** Each infusion will consist of a dose of 600 mg (2 vials of 30 mL) and will take 25 - 45 minutes (35 minutes ± 10 minutes).

- Maintenance phase:

- In the fifth week, your doctor will administer an intravenous infusion of diluted BEKEMV at a dose of 900 mg (3 vials of 30 mL) over a 25 – 45 minute (35 minutes ± 10 minutes) period.
- After the fifth week, your doctor will administer 900 mg of diluted BEKEMV every two weeks as a long-term treatment.

For children and adolescents:
- Children and adolescents with PNH and who are 40 kg weight and over are treated with the adult dosing.
- Children and adolescents with PNH and who are under 40 kg weight require a lower dose based on how much they weigh. Your doctor will calculate this.

For children and adolescents with PNH above 2 years of age and with body weight below 40 kg:

Patient body weight	**Initial phase**	**Maintenance phase**
30 to < 40 kg	600 mg weekly for the first 2 weeks	900 mg at week 3; then 900 mg every 2 weeks
20 to < 30 kg	600 mg weekly for the first 2 weeks	600 mg at week 3; then 600 mg every 2 weeks
10 to < 20 kg	600 mg single dose at week 1	300 mg at week 2; then 300 mg every 2 weeks

Patient body weight	Initial phase	Maintenance phase
5 to < 10 kg	300 mg single dose at week 1	300 mg at week 2; then 300 mg every 3 weeks

Following each infusion, you will be monitored for about one hour. Your doctor's instructions should be carefully observed.

If you receive more BEKEMV than you should

If you suspect that you have been accidentally administered a higher dose of BEKEMV than prescribed, please contact your doctor for advice.

If you forget an appointment to receive BEKEMV

If you forget an appointment, please contact your doctor immediately for advice and see section below "If you stop using BEKEMV".

If you stop using BEKEMV for PNH

Interrupting or ending treatment with BEKEMV may cause your PNH symptoms to come back more severely soon. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 8 weeks.

The risks of stopping BEKEMV include an increase in the destruction of your red blood cells, which may cause:
- A significant fall in your red blood cell counts (anaemia),
- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss the possible side effects with you and explain the benefits and risks of BEKEMV with you prior to treatment.

The most serious side effect was meningococcal sepsis. If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal and other *Neisseria* infections alert), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people)
- headache

Common (may affect up to 1 in 10 people)
- infection of the lung (pneumonia), common cold (nasopharyngitis), infection of the urinary system (urinary tract infection)
- low white blood cell count (leucopenia), reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- inability to sleep
- dizziness, high blood pressure

- upper respiratory tract infection, cough, throat pain (oropharyngeal pain), bronchitis, cold sores (herpes simplex)
- diarrhoea, vomiting, nausea, abdominal pain, rash, hair loss (alopecia), itchy skin (pruritus)
- pain in the joints (arms and legs), pain in the limbs (arms and legs)
- fever (pyrexia), feeling tired (fatigue), influenza like illness
- infusion related reaction

Uncommon (may affect up to 1 in 100 people)
- severe infection (meningococcal infection), sepsis, septic shock, viral infection, lower respiratory tract infection, stomach flu (gastrointestinal infection), cystitis
- infection, fungal infection, collection of pus (abscess), type of infection of the skin (cellulitis), influenza, sinusitis, tooth infection (abscess), gum infection
- relatively few platelets in blood (thrombocytopenia), low level of lymphocytes a specific type of white blood cells (lymphopenia), feeling your heartbeat
- serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction), hypersensitivity
- loss of appetite
- depression, anxiety, mood swings, sleep disorder
- tingling in part of the body (paraesthesia), shaking, taste disorders (dysgeusia), fainting
- vision blurred
- ringing in the ears, vertigo
- sudden and rapid development of extremely high blood pressure, low blood pressure, hot flush, vein disorder
- dyspnoea (difficulty breathing), nose bleed, stuffy nose (nasal congestion), throat irritation, runny nose (rhinorrhoea)
- inflammation of the peritoneum (the tissue that lines most of the organs of the abdomen), constipation, stomach discomfort after meals (dyspepsia), abdominal distension
- hives, redness of the skin, dry skin, red or purple spots under the skin, increased sweating, inflammation of the skin
- muscle cramp, muscle aches, back and neck pain, bone pain
- kidney disorder, difficulties or pain when urinating (dysuria), blood in urine
- spontaneous penile erection
- swelling (oedema), chest discomfort, feeling of weakness (asthaenia), chest pain, infusion site pain, chills
- increase of liver enzymes, decrease of the proportion of blood volume that is occupied by red blood cells, decrease in the protein in red blood cells that carries oxygen

Rare (may affect up to 1 in 1,000 people)
- infection by fungi (Aspergillus infection), infection of the joint (arthritis bacterial), *Haemophilus influenzae* infection, impetigo, bacterial sexual transmitted disease (gonorrhoea)
- skin tumour (melanoma), bone marrow disorder
- destruction of red blood cells (haemolysis), clumping of cells, abnormal clotting factor, abnormal blood clotting
- disease with thyroid overactivity (Basedow's disease)
- abnormal dreams
- irritation of eye
- bruise
- unusual backflow of food from stomach, gum pain
- yellowing of the skin and/or eyes (jaundice)
- skin colour disorder
- spasm of mouth muscle, joint swelling
- menstrual disorder
- abnormal leakage of the infused drug out of the vein, infusion site abnormal sensation, feeling hot

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BEKEMV

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

BEKEMV vials in the original package may be removed from refrigerated storage for only one single period of up to 7 days. At the end of this period the product can be put back in the refrigerator.
Store in the original package in order to protect from light. After dilution, the product should be used within 24 hours.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What BEKEMV contains

- The active substance is eculizumab (300 mg/30 mL in a vial corresponding to 10 mg/mL).

- The other ingredients are:
    - acetic acid,
    - sodium hydroxide,
    - disodium edetate (EDTA),
    - sorbitol (E420, see section 2 "BEKEMV contains sorbitol"),
    - polysorbate 80,
    - water for injections

What BEKEMV looks like and contents of the pack

BEKEMV is presented as a concentrate for solution for infusion (30 mL in a vial – pack size of 1).
BEKEMV is a clear to opalescent, colourless to slightly yellow solution.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Instructions for use for healthcare professionals handling BEKEMV

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

The following information is intended for healthcare professionals only:

1. How is BEKEMV supplied?

Each vial of BEKEMV contains 300 mg of active substance in 30 mL of product solution.

2. Before administration

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

BEKEMV should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Inspect visually BEKEMV solution for particulate matter and discolouration.
- Withdraw the required amount of BEKEMV from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute BEKEMV to a final concentration of 5 mg/mL (initial concentration divided by 2) by adding the appropriate amount of diluent to the infusion bag.
  - For 300 mg doses, use 30 mL of BEKEMV (10 mg/mL) and add 30 mL of diluent.
  - For 600 mg doses, use 60 mL of BEKEMV and add 60 mL of diluent.
  - For 900 mg doses, use 90 mL of BEKEMV and add 90 mL of diluent.

  The final volume of a 5 mg/mL diluted BEKEMV solution is 60 mL for 300 mg doses, 120 mL for 600 mg doses, 180 mL for 900 mg doses.

- Diluents are sodium chloride 9 mg/mL (0.9%) solution for injection, sodium chloride 4.5 mg/mL (0.45%) solution for injection or 5% glucose in water.
- Gently agitate the infusion bag containing the diluted BEKEMV solution to ensure thorough mixing of the medicinal product and diluent.
- The diluted solution should be allowed to warm to room temperature [18°C – 25°C] prior to administration by exposure to ambient temperature.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial.
- Diluted solution of BEKEMV may be stored at 2°C – 8°C for up to 24 hours prior to administration.

3. Administration

- Do not administer BEKEMV as an intravenous push or bolus injection.
- BEKEMV should only be administered via intravenous infusion.
- The diluted solution of BEKEMV should be administered by intravenous infusion over 25 to 45 minutes (35 minutes ± 10 minutes) in adults and 1 - 4 hours in paediatric patients under 18 years of age via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of BEKEMV from light during administration to the patient.

The patient 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 under 18 years of age.

4. Special handling and storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package in order to protect from light. BEKEMV vials in the original package may be removed from refrigerated storage for only one single period of up to 7 days. At the end of this period the product can be put back in the refrigerator.
Do not use this medicine after the expiry date which is stated on the carton and vial label after ‘EXP’. The expiry date refers to the last day of that month.