HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BKEMV safely and effectively. See full prescribing information for BKEMV.

BKEMV™ (eculizumab-aeeb) injection, for intravenous use
Initial U.S. Approval: 2024

BKEMV (eculizumab-aeeb) is biosimilar* to SOLIRIS® (eculizumab).

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Eculizumab products increase the risk of serious and life-threatening infections caused by *Neisseria meningitidis*.

- **Complete or update meningococcal vaccination at least 2 weeks prior to the first dose of BKEMV, unless the risks of delaying BKEMV outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients receiving a complement inhibitor. (5.1)**
- **Patients receiving eculizumab products are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of meningococcal infections and evaluate immediately if infection is suspected. (5.1)**

BKEMV is available only through a restricted program called BKEMV REMS. (5.2)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.3)	10/2024
Dosage and Administration, (2.4), (2.5)	10/2024

----------INDICATIONS AND USAGE----------

BKEMV is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. (1.1)
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. (1.2)

  Limitation of Use
  BKEMV is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive. (1.3)

----------DOSAGE AND ADMINISTRATION----------

For intravenous infusion only
PNH Dosage Regimen: (2.2)
aHUS Dosage Regimen: (2.3)
gMG Dosage Regimen: (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

BKEMV is contraindicated for initiation in patients with unresolved serious *Neisseria meningitidis* infection. (4)

----------WARNINGS AND PRECAUTIONS----------

- Use caution when administering BKEMV to patients with any other systemic infection. (5.3)
- Infusion-Related Reactions: Monitor patients during infusion, interrupt for reactions, and institute appropriate supportive measures. (5.6)

----------ADVERSE REACTIONS----------

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea. (6.1)

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20%) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, pyrexia. (6.1)

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

*****Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of BKEMV has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information**.**

Revised: 10/2024

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Eculizumab products, complement inhibitors, increase the risk of serious infections caused by *Neisseria meningitidis [see Warnings and Precautions (5.1)]*. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of BKEMV, unless the risks of delaying therapy with BKEMV outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving eculizumab products are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, BKEMV is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called BKEMV REMS [*see Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

BKEMV is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

1.2 Atypical Hemolytic Uremic Syndrome (aHUS)

BKEMV is indicated for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

Limitation of Use

BKEMV is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

1.3 Generalized Myasthenia Gravis (gMG)

BKEMV is indicated for treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis for Meningococcal Infection

Vaccinate patients against meningococcal infection (serogroups A, C, W, Y and B) according to current ACIP recommendations at least 2 weeks prior to initiation of BKEMV [*see Warnings and Precautions (5.1)*].

If urgent BKEMV therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible.

Healthcare providers who prescribe BKEMV must enroll in the BKEMV REMS *[see Warnings and Precautions (5.2)]*.

2.2 Recommended Dosage Regimen – PNH

For patients 18 years of age and older, BKEMV therapy consists of:
- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter.

Administer BKEMV at the recommended dosage regimen time points, or within two days of these time points *[see Warnings and Precautions (5.4)*].

2.3 Recommended Dosage Regimen – aHUS

For patients 18 years of age and older, BKEMV therapy consists of:
- 900 mg weekly for the first 4 weeks, followed by
- 1,200 mg for the fifth dose 1 week later, then
- 1,200 mg every 2 weeks thereafter.

For patients less than 18 years of age, administer BKEMV based upon body weight, according to the following schedule (Table 1):

Table 1: Dosing Recommendations in aHUS Patients Less Than 18 Years of Age

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly × 4 doses	1,200 mg at week 5; then 1,200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly × 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly × 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Administer BKEMV at the recommended dosage regimen time points, or within two days of these time points.

2.4 Recommended Dosage Regimen – gMG

For adult patients with generalized myasthenia gravis, BKEMV therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1,200 mg for the fifth dose 1 week later, then
- 1,200 mg every 2 weeks thereafter.

Administer BKEMV at the recommended dosage regimen time points, or within two days of these time points.

2.5 Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

For adult and pediatric patients with aHUS, and adult patients with gMG, supplemental dosing of BKEMV is required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion (PE/PI) (Table 2).

Table 2: Supplemental Dose of BKEMV after PE/PI

Type of Plasma Intervention	Most Recent BKEMV Dose	Supplemental BKEMV Dose with Each Plasma Intervention	Timing of Supplemental BKEMV Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	600 mg or greater	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	300 mg or greater	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

2.6 Preparation

Dilute BKEMV to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of BKEMV from the vial into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute BKEMV to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP to the infusion bag.

The final admixed BKEMV 5 mg/mL infusion volume is 60 mL for 300 mg doses, 120 mL for 600 mg doses, 180 mL for 900 mg doses or 240 mL for 1,200 mg doses (Table 3).

Table 3: Preparation and Reconstitution of BKEMV

BKEMV Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL

BKEMV Dose	Diluent Volume	Final Volume
900 mg	90 mL	180 mL
1,200 mg	120 mL	240 mL

Gently invert the infusion bag containing the diluted BKEMV solution to ensure thorough mixing of the product and diluent. Discard any unused portion left in a vial, as the product contains no preservatives.

Prior to administration, the admixture should be allowed to adjust to room temperature [18°C to 25°C (64°F to 77°F)]. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.7 Administration

Only administer as an intravenous infusion.

Do not administer as an intravenous push or bolus injection.

Administer the BKEMV admixture by intravenous infusion over 35 minutes in adults and 1 to 4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of BKEMV are stable for 64 hours at 2°C to 8°C (36°F to 46°F) or 24 hours at room temperature.

If an adverse reaction occurs during the administration of BKEMV, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion-related reaction.

3 DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) as a clear to opalescent and colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

BKEMV is contraindicated for initiation in patients with unresolved serious *Neisseria meningitidis* infection [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

Eculizumab products, complement inhibitors, increase a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. The initiation of BKEMV treatment is contraindicated in patients with unresolved serious *Neisseria meningitidis* infection.

Complete or update meningococcal vaccination (for serogroups A, C, W, Y and B) at least 2 weeks prior to administration of the first dose of BKEMV, according to current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with BKEMV. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information.

If urgent BKEMV therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including eculizumab products. The benefits and risks of treatment with BKEMV, as well as the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if these signs and symptoms occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of BKEMV in patients who are undergoing treatment for serious meningococcal infection, depending on the risks of interrupting treatment in the disease being treated.

BKEMV is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 BKEMV REMS

BKEMV is available only through a restricted program under a REMS called BKEMV REMS, because of the risk of serious meningococcal infections *[see Warnings and Precautions (5.1)]*.

Notable requirements of the BKEMV REMS include the following:

- Prescribers must enroll in the REMS.
- Prescribers must counsel patients about the risk of serious meningococcal infection.
- Prescribers must provide the patients with the REMS educational materials.
- Prescribers must assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y and B) and vaccinate if needed according to current ACIP recommendations 2 weeks prior to the first dose of BKEMV.
- Prescribers must provide a prescription for antibacterial drug prophylaxis if treatment must be started urgently and the patient is not up to date with meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of BKEMV.

- Healthcare settings and pharmacies that dispense BKEMV must be certified in the REMS and must verify prescribers are certified.

- Patients must receive counseling from the prescriber about the need to receive meningococcal vaccines per ACIP recommendations, the need to take antibiotics as directed by the prescriber, and the signs and symptoms of meningococcal infection.

- Patients must be instructed to carry the Patient Safety Card with them at all times during and for 3 months following treatment with BKEMV.

Further information is available at www.BKEMVREMS.com or 1-866-718-6927.

5.3 Other Infections

Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

Eculizumab products block terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections with *Neisseria meningitidis* but also *Streptococcus pneumoniae, Haemophilus influenzae,* and to a lesser extent, *Neisseria gonorrhoeae*. Additionally, *Aspergillus* infections have occurred in immunocompromised and neutropenic patients. Children treated with eculizumab products may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP recommendations. Patients receiving eculizumab products are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

5.4 Monitoring Disease Manifestations after BKEMV Discontinuation

Treatment Discontinuation for PNH

Monitor patients after discontinuing BKEMV for at least 8 weeks to detect hemolysis.

Treatment Discontinuation for aHUS

After discontinuing BKEMV, monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical trials, 18 patients (5 in the prospective studies) discontinued eculizumab treatment. TMA complications occurred following a missed dose in 5 patients, and eculizumab was reinitiated in 4 of these 5 patients.

Clinical signs and symptoms of TMA include changes in mental status, seizures, angina, dyspnea, or thrombosis. In addition, the following changes in laboratory parameters may identify a TMA complication: occurrence of two, or repeated measurement of any one of the following: a decrease in platelet count by 25% or more compared to baseline or the peak platelet count during BKEMV treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during BKEMV treatment; or, an increase in serum LDH by 25% or more over baseline or nadir during BKEMV treatment.

If TMA complications occur after BKEMV discontinuation, consider reinstitution of BKEMV treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI)], or appropriate organ-specific supportive measures.

5.5 Thrombosis Prevention and Management

The effect of withdrawal of anticoagulant therapy during eculizumab products treatment has not been established. Therefore, treatment with eculizumab products should not alter anticoagulant management.

5.6 Infusion-Related Reactions

Administration of eculizumab products may result in infusion-related reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion-related reaction which required discontinuation of eculizumab. Interrupt BKEMV infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections [*see Warnings and Precautions (5.1)*]
- Other Infections [*see Warnings and Precautions (5.3)*]
- Monitoring Disease Manifestations after BKEMV Discontinuation [*see Warnings and Precautions (5.4)*]
- Thrombosis Prevention and Management [*see Warnings and Precautions (5.5)*]
- Infusion-Related Reactions [*see Warnings and Precautions (5.6)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Meningococcal infections are the most important adverse reactions experienced by patients receiving eculizumab. In PNH clinical studies, two patients experienced meningococcal sepsis. Both patients had previously received a meningococcal vaccine. In clinical studies among patients without PNH, meningococcal meningitis occurred in one unvaccinated patient. Meningococcal sepsis occurred in one previously vaccinated patient enrolled in the retrospective aHUS study during the post-study follow-up period [*see Warnings and Precautions (5.1)*].

PNH

The data described below reflect exposure to eculizumab in 196 adult patients with PNH, age 18-85, of whom 55% were female. All had signs or symptoms of intravascular hemolysis. Eculizumab was studied in a placebo-controlled clinical study (PNH Study 1, in which 43 patients received eculizumab and 44, placebo); a single arm clinical study (PNH Study 2); and a long term extension study (E05-001). One hundred and eighty two patients were exposed for greater than one year. All patients received the recommended eculizumab dose regimen.

Table 4 summarizes the adverse reactions that occurred at a numerically higher rate in the eculizumab group than the placebo group and at a rate of 5% or more among patients treated with eculizumab.

Table 4: Adverse Reactions Reported in 5% or More of Eculizumab Treated Patients with PNH and Greater than Placebo in the Controlled Clinical Study

Reaction	eculizumab (N = 43) N (%)	Placebo (N = 44) N (%)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

In the placebo-controlled clinical study, serious adverse reactions occurred among 4 (9%) patients receiving eculizumab and 9 (21%) patients receiving placebo. The serious reactions included infections and progression of PNH. No deaths occurred in the study and no patients receiving eculizumab experienced a thrombotic event; one thrombotic event occurred in a patient receiving placebo.

Among 193 patients with PNH treated with eculizumab in the single arm, clinical study or the follow-up study, the adverse reactions were similar to those reported in the placebo-controlled clinical study. Serious adverse reactions occurred among 16% of the patients in these studies. The most common serious adverse reactions were: viral infection (2%), headache (2%), anemia (2%), and pyrexia (2%).

aHUS

The safety of eculizumab therapy in patients with aHUS was evaluated in four prospective, single-arm studies, three in adult and adolescent patients (Studies C08-002A/B, C08-003A/B, and C10-004), one in pediatric and adolescent patients (Study C10-003), and one retrospective study (Study C09-001r).

The data described below were derived from 78 adult and adolescent patients with aHUS in Studies C08-002A/B, C08-003A/B and C10-004. All patients received the recommended dosage of eculizumab. Median exposure was 67 weeks (range: 2-145 weeks). Table 5 summarizes all adverse events reported in at least 10% of patients in Studies C08-002A/B, C08-003A/B and C10-004 combined.

Table 5: Per Patient Incidence of Adverse Events in 10% or More Adult and Adolescent Patients Enrolled in Studies C08-002A/B, C08-003A/B and C10-004 Separately and in Total

	Number (%) of Patients			
	C08-002A/B (N=17)	C08-003A/B (N=20)	C10-004 (N=41)	Total (N=78)
Vascular Disorders				
Hypertension[a]	10 (59)	9 (45)	7 (17)	26 (33)
Hypotension	2 (12)	4 (20)	7 (17)	13 (17)
Infections and Infestations				
Bronchitis	3 (18)	2 (10)	4 (10)	9 (12)

	Number (%) of Patients			
	C08-002A/B (N=17)	C08-003A/B (N=20)	C10-004 (N=41)	Total (N=78)
Nasopharyngitis	3 (18)	11 (55)	7 (17)	21 (27)
Gastroenteritis	3 (18)	4 (20)	2 (5)	9 (12)
Upper respiratory tract infection	5 (29)	8 (40)	2 (5)	15 (19)
Urinary tract infection	6 (35)	3 (15)	8 (20)	17 (22)
Gastrointestinal Disorders				
Diarrhea	8 (47)	8 (40)	12 (32)	29 (37)
Vomiting	8 (47)	9 (45)	6 (15)	23 (30)
Nausea	5 (29)	8 (40)	5 (12)	18 (23)
Abdominal pain	3 (18)	6 (30)	6 (15)	15 (19)
Nervous System Disorders				
Headache	7 (41)	10 (50)	15 (37)	32 (41)
Blood and Lymphatic System Disorders				
Anemia	6 (35)	7 (35)	7 (17)	20 (26)
Leukopenia	4 (24)	3 (15)	5 (12)	12 (15)
Psychiatric Disorders				
Insomnia	4 (24)	2 (10)	5 (12)	11 (14)
Renal and Urinary Disorders				
Renal Impairment	5 (29)	3 (15)	6 (15)	14 (18)
Proteinuria	2 (12)	1 (5)	5 (12)	8 (10)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	4 (24)	6 (30)	8 (20)	18 (23)
General Disorders and Administration Site Conditions				
Fatigue	3 (18)	4 (20)	3 (7)	10 (13)
Peripheral edema	5 (29)	4 (20)	9 (22)	18 (23)
Pyrexia	4 (24)	5 (25)	7 (17)	16 (21)
Asthenia	3 (18)	4 (20)	6 (15)	13 (17)
Eye Disorder	5 (29)	2 (10)	8 (20)	15 (19)
Metabolism and Nutrition Disorders				
Hypokalemia	3 (18)	2 (10)	4 (10)	9 (12)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (6)	6 (30)	1 (20)	8 (10)
Skin and Subcutaneous Tissue Disorders				
Rash	2 (12)	3 (15)	6 (15)	11 (14)
Pruritus	1 (6)	3 (15)	4 (10)	8 (10)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1 (6)	2 (10)	7 (17)	10 (13)
Back pain	3 (18)	3 (15)	2 (5)	8 (10)

[a.] includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

In Studies C08-002A/B, C08-003A/B and C10-004 combined, 60% (47/78) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were infections (24%), hypertension (5%), chronic renal failure (5%), and renal impairment (5%). Five patients discontinued eculizumab due to adverse events; three due to worsening renal function, one due to new diagnosis of Systemic Lupus Erythematosus, and one due to meningococcal meningitis.

Study C10-003 included 22 pediatric and adolescent patients, of which 18 patients were less than 12 years of age. All patients received the recommended dosage of eculizumab. Median exposure was 44 weeks (range: 1 dose-87 weeks).

Table 6 summarizes all adverse events reported in at least 10% of patients enrolled in Study C10-003.

Table 6: Per Patient Incidence of Adverse Reactions in 10% or More Patients Enrolled in Study C10-003

	1 month to <12 yrs (N=18)	Total (N=22)
Eye Disorders	3 (17)	3 (14)
Gastrointestinal Disorders		
Abdominal pain	6 (33)	7 (32)
Diarrhea	5 (28)	7 (32)
Vomiting	4 (22)	6 (27)
Dyspepsia	0	3 (14)
General Disorders and Administration Site Conditions		
Pyrexia	9 (50)	11 (50)
Infections and Infestations		
Upper respiratory tract infection	5 (28)	7 (32)
Nasopharyngitis	3 (17)	6 (27)
Rhinitis	4 (22)	4 (18)
Urinary Tract infection	3 (17)	4 (18)
Catheter site infection	3 (17)	3 (14)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2 (11)	3 (14)
Nervous System Disorders		
Headache	3 (17)	4 (18)
Renal and Urinary Disorders	3 (17)	4 (18)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	7 (39)	8 (36)
Oropharyngeal pain	1 (6)	3 (14)
Skin and Subcutaneous Tissue Disorders		
Rash	4 (22)	4 (18)
Vascular Disorders		
Hypertension	4 (22)	4 (18)

In Study C10-003, 59% (13/22) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were hypertension (9%), viral gastroenteritis (9%), pyrexia (9%), and upper respiratory infection (9%). One patient discontinued eculizumab due to an adverse event (severe agitation).

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in Study C09-001r (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. Study C09-001r included 19 pediatric patients less than 18 years of age. Overall, the safety of eculizumab in pediatric patients with aHUS enrolled in Study C09-001r appeared similar to that observed in adult patients. The most common (≥15%) adverse events occurring in pediatric patients are presented in Table 7.

Table 7: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in Study C09-001r

	Number (%) of Patients			
	<2 yrs (N=5)	2 to <12 yrs (N=10)	12 to <18 yrs (N=4)	Total (N=19)
General Disorders and Administration Site Conditions				
Pyrexia	4 (80)	4 (40)	1 (25)	9 (47)
Gastrointestinal Disorders				
Diarrhea	1 (20)	4 (40)	1 (25)	6 (32)
Vomiting	2 (40)	1 (10)	1 (25)	4 (21)
Infections and Infestations				
Upper respiratory tract infection[a]	2 (40)	3 (30)	1 (25)	6 (32)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3 (60)	2 (20)	0 (0)	5 (26)
Nasal congestion	2 (40)	2 (20)	0 (0)	4 (21)
Cardiac Disorders				
Tachycardia	2 (40)	2 (20)	0 (0)	4 (21)

[a.] includes the preferred terms upper respiratory tract infection and nasopharyngitis.

Generalized Myasthenia Gravis (gMG)

In a 26-week placebo-controlled trial evaluating the effect of eculizumab for the treatment of gMG (gMG Study 1), 62 patients received eculizumab at the recommended dosage regimen and 63 patients received placebo *[see Clinical Studies (14.3)]*. Patients were 19 to 79 years of age, and 66% were female. Table 8 displays the most common adverse reactions from gMG Study 1 that occurred in ≥ 5% of eculizumab-treated patients and at a greater frequency than on placebo.

Table 8: Adverse Reactions Reported in 5% or More of Eculizumab-Treated Patients in gMG Study 1 and at a Greater Frequency than in Placebo-Treated Patients

	eculizumab (N=62) N(%)	Placebo (N=63) N(%)
Gastrointestinal Disorders		
Abdominal pain	5 (8)	3 (5)
General Disorders and Administration Site Conditions		
Peripheral edema	5 (8)	3 (5)
Pyrexia	4 (7)	2 (3)
Infections and Infestations		
Herpes simplex virus infections	5 (8)	1 (2)
Injury, Poisoning, and Procedural Complications		
Contusion	5 (8)	2 (3)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	9 (15)	5 (8)

The most common adverse reactions (≥ 10%) that occurred in eculizumab-treated patients in the long-term extension to gMG Study 1, Study ECU-MG-302, and that are not included in Table 8 were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of eculizumab products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to eculizumab products exposure.

Adverse Reactions from Postmarketing Spontaneous Reports

- Fatal or serious infections: *Neisseria gonorrhoeae, Neisseria meningitidis, Neisseria sicca/subflava, Neisseria spp* unspecified.
- Cases of cholestatic or mixed pattern liver injury with increased serum liver enzymes and bilirubin levels have been reported in adult and pediatric patients with aHUS who were treated with eculizumab. These events occurred within 3 to 27 days after starting treatment. The median time to resolution (or return to baseline) was approximately 3 weeks.

7 DRUG INTERACTIONS

7.1 Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

Concomitant use of eculizumab products with plasma exchange (PE), plasmapheresis (PP) or fresh frozen plasma infusion (PE/PI) treatment can reduce serum eculizumab products concentrations and requires a supplement dose of BKEMV *[see Dosage and Administration (2.5)]*.

7.2 Neonatal Fc Receptor Blockers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data on outcomes of pregnancies that have occurred following eculizumab use in pregnant women have not identified a concern for specific adverse developmental outcomes (*see Data*). There are risks to the mother and fetus associated with untreated paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) in pregnancy (*see Clinical Considerations*). Animal studies using a mouse analogue of the eculizumab molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

aHUS in pregnancy is associated with adverse maternal outcomes, including pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including intrauterine growth restriction (IUGR), fetal death and low birth weight.

Data

Human Data

A pooled analysis of prospectively (50.3%) and retrospectively (49.7%) collected data in more than 300 pregnant women with live births following exposure to eculizumab have not suggested safety concerns. However, these data cannot definitively exclude any drug-associated risk during pregnancy, because of the limited sample size.

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 2-4 times (low dose) and 4-8 times (high dose) the recommended human eculizumab dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. 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; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function.

8.2 Lactation

Risk Summary

Although limited published data does not report detectable levels of eculizumab in human milk, maternal IgG is known to be present in human milk. Available information is insufficient to inform the effect of eculizumab products on the breastfed infant. There are no data on the effects of eculizumab products on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BKEMV and any potential adverse effects on the breastfed child from BKEMV or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of BKEMV for the treatment of PNH, or gMG in pediatric patients have not been established.

The safety and effectiveness of BKEMV for the treatment of aHUS have been established in pediatric patients. Use of BKEMV in pediatric patients for this indication is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of eculizumab for the treatment of aHUS. The studies included a total of 47 pediatric patients (ages 2 months to 17 years). The safety and effectiveness of eculizumab for the treatment of aHUS appear similar in pediatric and adult patients [*see Adverse Reactions (6.1), and Clinical Studies (14.2)*].

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to ACIP guidelines [*see Warnings and Precautions (5.1, 5.3)*].

8.5 Geriatric Use

Fifty-one patients 65 years of age or older (15 with PNH, 4 with aHUS, 26 with gMG, and 6 with another indication) were treated with eculizumab in clinical trials in the approved indications. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

11 DESCRIPTION

Eculizumab-aeeb, a complement inhibitor, is a recombinant humanized monoclonal IgG2/4κ antibody produced by Chinese Hamster Ovary (CHO) cell culture and purified by standard bioprocess technology. Eculizumab-aeeb contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. Eculizumab-aeeb 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.

BKEMV (eculizumab-aeeb) injection is a sterile, clear to opalescent, colorless to slightly yellow, preservative-free 10 mg/mL solution for intravenous infusion and is supplied in 30-mL single-dose vials. The product is formulated at pH 5.2 and each 30 mL vial contains 300 mg of eculizumab-aeeb, sorbitol (E420) (1500 mg), acetic acid (18.0 mg), polysorbate 80 (3.0 mg) (vegetable origin), edetate disodium (EDTA) (0.6 mg), sodium hydroxide may be added to adjust pH, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eculizumab-aeeb, the active ingredient in BKEMV, is a monoclonal antibody 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 products inhibit terminal complement-mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

The precise mechanism by which eculizumab exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

12.2 Pharmacodynamics

In the placebo-controlled clinical study (PNH Study 1), eculizumab when administered as recommended reduced serum LDH levels from 2200 ± 1034 U/L (mean ± SD) at baseline to 700 ± 388 U/L by week one and maintained the effect through the end of the study at week 26 (327 ± 433 U/L) in patients with PNH. In the single arm clinical study (PNH Study 2), the effect was maintained through week 52 [*see Clinical Studies (14)*].

In patients with PNH, aHUS, and gMG, free C5 concentrations of <0.5 mcg/mL was correlated with complete blockade of terminal complement activity.

12.3 Pharmacokinetics

Following intravenous maintenance doses of 900 mg once every 2 weeks in patients with PNH, the week 26 observed mean ± SD serum eculizumab maximum concentration (C_{max}) was 194 ± 76 mcg/mL and the trough concentration (C_{trough}) was 97 ± 60 mcg/mL. Following intravenous maintenance doses of 1,200 mg once every 2 weeks in patients with aHUS, the week 26 observed mean ± SD C_{trough} was 242 ± 101 mcg/mL. Following intravenous maintenance doses of 1,200 mg once every 2 weeks in patients with gMG, the week 26 observed mean ± SD C_{max} was 783 ± 288 mcg/mL and the C_{trough} was 341 ± 172 mcg/mL.

Steady state was achieved 4 weeks after starting eculizumab treatment, with accumulation ratio of approximately 2-fold in all studied indications. Population pharmacokinetic analyses showed that eculizumab pharmacokinetics were dose-linear and time-independent over the 600 mg to 1,200 mg dose range, with inter-individual variability of 21% to 38%.

Distribution

The eculizumab volume of distribution for a typical 70 kg patient was 5 L to 8 L.

Elimination

The half-life of eculizumab was approximately 270 hours to 414 hours.

Plasma exchange or infusion increased the clearance of eculizumab by approximately 250-fold and reduced the half-life to 1.26 hours. Supplemental dosing is recommended when BKEMV is administered to patients receiving plasma exchange or infusion [*see Dosage and Administration (2.5)*].

Specific Populations

Age, Sex, and Race:

The pharmacokinetics of eculizumab were not affected by age (2 months to 85 years), sex, or race.

Renal Impairment:

Renal function did not affect the pharmacokinetics of eculizumab in PNH (creatinine clearance of 8 mL/min to 396 mL/min calculated using Cockcroft-Gault formula) or aHUS (estimated glomerular filtration rate [eGFR] of 5 mL/min/1.73 m^2 to105 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease [MDRD] formula, or gMG patients (eGFR of 44 mL/min/1.73 m^2 to 168 mL/min/1.73 m^2 using MDRD formula).

12.6 IMMUNOGENICITY

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of eculizumab or of other eculizumab products.

The immunogenicity of eculizumab has been evaluated using two different immunoassays for the detection of anti-eculizumab antibodies: a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target was used for the PNH indication; and an electro-chemiluminescence (ECL) bridging assay using the eculizumab whole molecule as target was used for the aHUS, and gMG indications, as well as for additional patients with PNH. In the PNH population, antibodies to eculizumab were detected in 3/196 (2%) patients using the ELISA assay and in 5/161 (3%) patients using the ECL assay during the entire treatment period. In the aHUS population, antibodies to eculizumab were detected in 3/100 (3%) patients using the ECL assay during the entire treatment period. None of the 62 patients with gMG had antibodies to eculizumab detected following the 26-week active treatment.

An ECL based neutralizing assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 5 patients with PNH and the 3 patients with aHUS, with anti-eculizumab antibody positive samples using the ECL assay. Two of 161 patients with PNH (1.2%) and 1 of 100 patients with aHUS (1%) had low positive values for neutralizing antibodies.

No apparent correlation of antibody development to clinical response was observed

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of eculizumab products have not been conducted.

Genotoxicity studies have not been conducted with eculizumab products.

Effects of eculizumab products upon fertility have not been studied in animals. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 4-8 times the equivalent of the clinical dose of eculizumab had no adverse effects on mating or fertility.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of eculizumab in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26-week study (PNH Study 1, NCT00122330); PNH patients were also treated with eculizumab in a single arm 52-week study (PNH Study 2, NCT00122304) and in a long-term

extension study (E05-001, NCT00122317). Patients received meningococcal vaccination prior to receipt of eculizumab. In all studies, the dose of eculizumab was 600 mg study drug 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.

PNH Study 1:

PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either eculizumab (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin 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. Endpoints related to hemolysis included the numbers of patients achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26-week period. Hemolysis 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 medications.

Major baseline characteristics were balanced (see Table 9).

Table 9: PNH Study 1 Patient Baseline Characteristics

Parameter	Study 1	
	Placebo (N=44)	**eculizumab (N=43)**
Mean age (SD)	38 (13)	42 (16)
Gender - female (%)	29 (66)	23 (54)
History of aplastic anemia or myelodysplastic syndrome (%)	12 (27)	8 (19)
Patients with history of thrombosis (events)	8 (11)	9 (16)
Concomitant anticoagulants (%)	20 (46)	24 (56)
Concomitant steroids/immunosuppressant treatments (%)	16 (36)	14 (33)
Packed RBC units transfused per patient in previous 12 months (median (Q1, Q3))	17 (14, 25)	18 (12, 24)
Mean Hgb level (g/dL) at setpoint (SD)	8 (1)	8 (1)
Pre-treatment LDH levels (median, U/L)	2,234	2,032
Free hemoglobin at baseline (median, mg/dL)	46	41

Patients treated with eculizumab had significantly reduced ($p< 0.001$) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 10). 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 products on thrombotic events could not be determined.

Table 10: PNH Study 1 Results

	Placebo (N=44)	eculizumab (N=43)
Percentage of patients with stabilized hemoglobin levels	0	49
Packed RBC units transfused per patient (median)	10	0
(range)	(2 - 21)	(0 - 16)
Transfusion avoidance (%)	0	51
LDH levels at end of study (median, U/L)	2,167	239
Free hemoglobin at end of study (median, mg/dL)	62	5

PNH Study 2 and Extension Study:

PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter received eculizumab over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Overall, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. One hundred and eighty-seven eculizumab-treated PNH patients were enrolled in a long term extension study. All patients sustained a reduction in intravascular hemolysis 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, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during eculizumab products therapy was not studied [*see Warnings and Precautions (5.5)*].

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Five single-arm studies [four prospective: C08-002A/B (NCT00844545 and NCT00844844), C08-003A/B (NCT00838513 and NCT00844428), C10-003 (NCT01193348), and C10-004 (NCT01194973); and one retrospective: C09-001r (NCT01770951)] evaluated the safety and efficacy of eculizumab for the treatment of aHUS. Patients with aHUS received meningococcal vaccination prior to receipt of eculizumab or received prophylactic treatment with antibiotics until 2 weeks after vaccination. In all studies, the dose of eculizumab in adult and adolescent patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1,200 mg 7 ± 2 days later, then 1,200 mg every 14 ± 2 days thereafter. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in Study C09-001r and Study C10-003 was based on body weight [*see Dosage and Administration (2.3)*]. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Endpoints related to TMA included the following:

- platelet count change from baseline
- hematologic normalization *(maintenance of normal platelet counts and LDH levels for at least four weeks)*
- complete TMA response *(hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks)*
- TMA-event free status *(absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement)*
- Daily TMA intervention rate *(defined as the number of plasma exchange or plasma infusion interventions and the number of new dialyses required per patient per day).*

aHUS Resistant to PE/PI (Study C08-002A/B)

Study C08-002A/B enrolled patients who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, patients were required to have a platelet count ≤150 × 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in Study C08-002A/B were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 70%-121%. Seventy-six percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 11 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-002A/B.

Table 11: Baseline Characteristics of Patients Enrolled in Study C08-002A/B

Parameter	C08-002A/B (N=17)
Time from aHUS diagnosis until screening in months, median (min, max)	10 (0.26, 236)
Time from current clinical TMA manifestation until screening in months, median (min, max)	<1 (<1, 4)
Baseline platelet count (× 10^9/L), median (range)	118 (62, 161)
Baseline LDH (U/L), median (range)	269 (134, 634)

Patients in Study C08-002A/B received eculizumab for a minimum of 26 weeks. In Study C08-002A/B, the median duration of eculizumab therapy was approximately 100 weeks (range: 2 weeks to 145 weeks).

Renal function, as measured by eGFR, was improved and maintained during eculizumab therapy. The mean eGFR (± SD) increased from 23 ± 15 mL/min/1.73 m^2 at baseline to 56 ± 40 mL/min/1.73 m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73 m^2). Four of the five patients who required dialysis at baseline were able to discontinue dialysis.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of eculizumab. Eculizumab reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C08-002A/B, mean platelet count (± SD) increased from 109 ± 32 × 10^9/L at baseline to 169 ± 72 × 10^9/L by one week; this effect was maintained through 26 weeks (210 ± 68 × 10^9/L), and 2 years (205 ± 46 × 10^9/L). When treatment was continued for more than 26 weeks, two additional patients achieved Hematologic Normalization as well as Complete TMA response. Hematologic Normalization and Complete TMA response were maintained by all responders. In Study C08-002A/B, responses to eculizumab were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 12 summarizes the efficacy results for Study C08-002A/B.

Table 12: Efficacy Results for Study C08-002A/B

Efficacy Parameter	Study C08-002A/B at 26 wks[1] (N=17)	Study C08-002A/B at 2 yrs[2] (N=17)
Complete TMA response, n (%) Median Duration of complete TMA response, weeks (range)	11 (65) 38 (25, 56)	13 (77) 99 (25, 139)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%) Median duration of eGFR improvement, days (range)	9 (53) 251 (70, 392)	10 (59) ND

Hematologic normalization, n (%) Median Duration of hematologic normalization, weeks (range)	13 (76) 37 (25, 62)	15 (88) 99 (25, 145)
TMA eventfree status, n (%)	15 (88)	15 (88)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.82 (0.04, 1.52) 0 (0, 0.31)	 0.82 (0.04, 1.52) 0 (0, 0.36)

[1.] At data cut-off (September 8, 2010).
[2.] At data cut-off (April 20, 2012).

aHUS Sensitive to PE/PI (Study C08-003A/B)

Study C08003A/B enrolled patients undergoing chronic PE/PI who generally did- not display hematologic signs of ongoing thrombotic microangiopathy (TMA). All patients had received PT at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first eculizumab dose. Patients on chronic dialysis were permitted to enroll in Study C08-003A/B. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in Study C08003A/B were required to have ADAMTS13 activity level above 5%; observed- range of values in the trial were 37%-118%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 13 summarizes the key baseline clinical and diseaserelated- characteristics of patients enrolled in Study C08-003A/B.

Table 13: Baseline Characteristics of Patients Enrolled in Study C08-003A/B

Parameter	Study C08-003A/B (N=20)
Time from aHUS diagnosis until screening in months, median (min, max)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	9 (1, 45)
Baseline platelet count ($\times 10^9$/L), median (range)	218 (105, 421)
Baseline LDH (U/L), median (range)	200 (151, 391)

Patients in Study C08-003A/B received eculizumab for a minimum of 26 weeks. In Study C08-003A/B, the median duration of eculizumab therapy was approximately 114 weeks (range: 26 to 129 weeks).

Renal function, as measured by eGFR, was maintained during eculizumab therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73 m^2 at baseline, and was maintained through 26 weeks (37 ± 21 mL/min/1.73 m^2) and 2 years (40 ± 18 mL/min/1.73 m^2). No patient required new dialysis with eculizumab.

Reduction in terminal complement activity was observed in all patients after the commencement of eculizumab. Eculizumab reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 × 10^9/L at baseline, 233 ± 69 × 10^9/L at week 26, and 224 ± 52 × 10^9/L at 2 years. When treatment was continued for more than 26 weeks, six additional patients achieved Complete TMA response. Complete TMA Response and Hematologic Normalization were maintained by all responders. In Study C08-003A/B, responses to eculizumab were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 14 summarizes the efficacy results for Study C08-003A/B.

Table 14: Efficacy Results for Study C08-003A/B

Efficacy Parameter	Study C08-003A/B at 26 wks[1] (N=20)	Study C08-003A/B at 2 yrs[2] (N=20)
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range)	5 (25) 32 (12, 38)	11 (55) 68 (38, 109)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	1 (5)	8 (40)
TMA Eventfree status n (%)	16 (80)	19 (95)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.23 (0.05, 1.07) 0	 0.23 (0.05, 1.07) 0 (0, 0.01)
Hematologic normalization[4], n (%) Median duration of hematologic normalization, weeks (range)[3]	18 (90) 38 (22, 52)	18 (90) 114 (33, 125)

1. At data cut-off (September 8, 2010).
2. At data cut-off (April 20, 2012).
3. Calculated at each post-dose day of measurement (excluding Days 1 to 4) using a repeated measurement ANOVA model.
4. In Study C08-003A/B, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PE/PI.

Retrospective Study in Patients with aHUS (C09-001r)

The efficacy results for the aHUS retrospective study (Study C09-001r) were generally consistent with results of the two prospective studies. Eculizumab reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 × 10^9/L at baseline to 233 ±10^9 × 10^9/L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 254 ± 79 × 10^9/L).

A total of 19 pediatric patients (ages 2 months to 17 years) received eculizumab in Study C09-001r. The median duration of eculizumab therapy was 16 weeks (range 4 to 70 weeks) for children < 2 years of age (n=5), 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for patients 12 to < 18 years of age (n=4). Fifty-three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody.

Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in Studies C08-002A/B and C08-003A/B (Table 15). No pediatric patient required new dialysis during treatment with eculizumab.

Table 15: Efficacy Results in Pediatric Patients Enrolled in Study C09-001r

Efficacy Parameter	<2 yrs (N=5)	2 to <12 yrs (N=10)	12 to <18 yrs (N=4)	Total (N=19)
Complete TMA response, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)[2]	2 (40)	6 (60)	1 (25)	9 (47)
Platelet count normalization, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Hematologic Normalization, n (%)	2 (40)	5 (50)	1 (25)	8 (42)

Efficacy Parameter	<2 yrs (N=5)	2 to <12 yrs (N=10)	12 to <18 yrs (N=4)	Total (N=19)
Daily TMA intervention rate, median (range)				
Before eculizumab	1 (0, 2)	<1 (0.07, 1.46)	<1 (0, 1)	0.31 (0.00, 2.38)
On eculizumab treatment	<1 (0, <1)	0 (0, <1)	0 (0, <1)	0.00 (0.00 , 0.08)

[1.] Platelet count normalization was defined as a platelet count of at least 150,000 × 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.

[2.] Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period and another received eculizumab as prophylaxis following renal allograft transplantation.

Adult Patients with aHUS (Study C10-004)

Study C10-004 enrolled patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrollment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in Study C10-004 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28%-116%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab. Table 16 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

Table 16: Baseline Characteristics of Patients Enrolled in Study C10-004

Parameter	Study C10-004 (N=41)
Time from aHUS diagnosis until start of study drug in months, median (range)	0.79 (0.03 – 311)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.52 (0.03–19)
Baseline platelet count (× 10^9/L), median (range)	125 (16 – 332)
Baseline LDH (U/L), median (range)	375 (131 – 3318)

Patients in Study C10-004 received eculizumab for a minimum of 26 weeks. In Study C10-004, the median duration of eculizumab therapy was approximately 50 weeks (range: 13 weeks to 86 weeks).

Renal function, as measured by eGFR, was improved during eculizumab therapy. The mean eGFR (± SD) increased from 17 ± 12 mL/min/1.73 m^2 at baseline to 47 ± 24 mL/min/1.73 m^2 by 26 weeks. Twenty of the 24 patients who required dialysis at study baseline were able to discontinue dialysis during eculizumab treatment.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of eculizumab. Eculizumab reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C10-004, mean platelet count (± SD) increased from 119 ± 66 × 10^9/L at baseline to 200 ± 84 × 10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 252 ± 70 × 10^9/L). In Study C10-004, responses to eculizumab were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 17 summarizes the efficacy results for Study C10-004.

Table 17: Efficacy Results for Study C10-004

Efficacy Parameter	Study C10-004 (N=41)
Complete TMA response, n (%), 95% CI Median duration of complete TMA response, weeks (range)	23 (56) 40,72 42 (6, 75)
Patients with eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	22 (54)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range)	36 (88) 46 (10, 75)
TMA Eventfree Status, n (%)	37 (90)
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

Pediatric and Adolescent Patients with aHUS (Study C10-003)

Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥ 97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 (range: 5 months to 17 years). Patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 18 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

Table 18: Baseline Characteristics of Patients Enrolled in Study C10-003

Parameter	Patients 1 month to <12 years (N=18)	All Patients (N=22)
Time from aHUS diagnosis until start of study drug in months, median (range)	0.51 (0.03-58)	0.56 (0.03-191)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.23 (0.03-4)	0.2 (0.03-4)
Baseline platelet count (× 10^9/L), median (range)	110 (19-146)	91 (19-146)
Baseline LDH (U/L) median (range)	1510 (282-7164)	1244 (282-7164)

Patients in Study C10-003 received eculizumab for a minimum of 26 weeks. In Study C10-003, the median duration of eculizumab therapy was approximately 44 weeks (range: 1 dose to 88 weeks).

Renal function, as measured by eGFR, was improved during eculizumab therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73 m^2 at baseline to 98 ± 44 mL/min/1.73 m^2 by 26 weeks. Among the 20 patients with a CKD stage ≥2 at baseline, 17 (85%) achieved a CKD improvement of ≥1 stage. Among the 16 patients ages 1 month to <12 years with a CKD stage ≥2 at baseline, 14 (88%) achieved a CKD improvement by ≥1 stage. Nine of the 11 patients who required dialysis at study baseline were able to discontinue dialysis during eculizumab treatment. Responses were observed across all ages from 5 months to 17 years of age.

Reduction in terminal complement activity was observed in all patients after commencement of eculizumab. Eculizumab reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ±

42×10^9/L at baseline to 281 ± 123 × 10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 × 10^9/L). In Study C10-003, responses to eculizumab were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 19 summarizes the efficacy results for Study C10-003.

Table 19: Efficacy Results for Study C10-003

Efficacy Parameter	Patients 1 month to <12 years (N=18)	All Patients (N=22)
Complete TMA response, n (%) 95% CI Median Duration of complete TMA response, weeks (range)[1]	11 (61) 36, 83 40 (14, 77)	14 (64) 41, 83 37 (14, 77)
eGFR improvement ≥15 mL/min/1.73•m^2•n (%)	16 (89)	19 (86)
Complete Hematologic Normalization, n (%) Median Duration of complete hematologic normalization, weeks (range)	14 (78) 38 (14, 77)	18 (82) 38 (14, 77)
TMA Event-Free Status, n (%)	17 (94)	21 (95)
Daily TMA Intervention rate, median (range) Before eculizumab treatment On eculizumab treatment	 0.2 (0, 1.7) 0 (0, 0.01)	 0.4 (0, 1.7) 0 (0, 0.01)

[1.] Through data cutoff (October 12, 2012).

14.3 Generalized Myasthenia Gravis (gMG)

The efficacy of eculizumab for the treatment of gMG was established in gMG Study 1 (NCT01997229), a 26-week randomized, double-blind, parallel-group, placebo-controlled, multi-center trial that enrolled patients who met the following criteria at screening:

1. Positive serologic test for anti-AChR antibodies,
2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV,
3. MG-Activities of Daily Living (MG-ADL) total score ≥ 6,
4. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIg).

A total of 62 patients were randomized to receive eculizumab treatment and 63 were randomized to receive placebo. Baseline characteristics were similar between treatment groups, including age at diagnosis (38 years in each group), gender [66% female (eculizumab) versus 65% female (placebo)], and duration of gMG [9.9 (eculizumab) versus 9.2 (placebo) years]. Over 95% of patients in each group were receiving acetylcholinesterase (AchE) inhibitors, and 98% were receiving immunosuppressant therapies (ISTs). Approximately 50% of each group had been previously treated with at least 3 ISTs.

Eculizumab was administered according to the recommended dosage regimen *[see Dosage and Administration (2.4)]*.

The primary efficacy endpoint for gMG Study 1 was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8

signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function (total score 0-24). A statistically significant difference favoring eculizumab was observed in the mean change from baseline to Week 26 in MG-ADL total scores [-4.2 points in the eculizumab-treated group compared with -2.3 points in the placebo-treated group (p=0.006)].

A key secondary endpoint in gMG Study 1 was the change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at Week 26. The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness (total score 0-39). A statistically significant difference favoring eculizumab was observed in the mean change from baseline to Week 26 in QMG total scores [-4.6 points in the eculizumab-treated group compared with -1.6 points in the placebo-treated group (p=0.001)].

The results of the analysis of the MG-ADL and QMG from gMG Study 1 are shown in Table 20.

Table 20: Analysis of Change from Baseline to Week 26 in MG-ADL and QMG Total Scores in gMG Study 1

Efficacy Endpoints	Eculizumab-LS Mean (N=62) (SEM)	Placebo-LS Mean (N=63) (SEM)	Eculizumab change relative to placebo – LS Mean Difference (95% CI)	p-values
MG-ADL	−4.2 (0.49)	−2.3 (0.48)	−1.9 (-3.3, −0.6)	(0.006[a], 0.014[b])
QMG	−4.6 (0.60)	−1.6 (0.59)	−3.0 (-4.6, −1.3)	(0.001[a], 0.005[b])

SEM= Standard Error of the Mean;
Eculizumab-LSMean = least square mean for the treatment group;
Placebo-LSMean = least square mean for the placebo group;
LSMean-Difference (95% CI) = Difference in least square mean with 95% confidence interval;
p-values (testing the null hypothesis that there is no difference between the two treatment arms
a: in least square means at Week 26 using a repeated measure analysis; b: in ranks at Week 26 using a worst rank analysis)

In gMG Study 1, a clinical response was defined in the MG-ADL total score as at least a 3-point improvement and in QMG total score as at least a 5-point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was statistically significantly higher for eculizumab compared to placebo for both measures. For both endpoints, and also at higher response thresholds (≥ 4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥ 6-, 7-, 8-, 9-, or 10-point improvement on QMG), the proportion of clinical responders was consistently greater for eculizumab compared to placebo. Available data suggest that clinical response is usually achieved by 12 weeks of eculizumab treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

BKEMV (eculizumab-aeeb) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution supplied as one 300 mg/30 mL (10 mg/mL) single-dose vial per carton (NDC 55513-180-01).

Store BKEMV vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. BKEMV vials may be stored in the original carton at controlled room temperature [not more than 25°C (77°F)] for only a single period up to 7 days. Do not use beyond the expiration date stamped on the carton. Refer to *Dosage and Administration (2)* for information on the stability and storage of diluted solutions of BKEMV.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Medication Guide).

Serious Meningococcal Infections

Advise patients of the risk of serious meningococcal infection.

Inform patients of the need to complete or update their meningococcal vaccinations at least 2 weeks prior to receiving the first dose of BKEMV or receive antibacterial drug prophylaxis if BKEMV treatment must be initiated immediately and they have not been previously vaccinated. Inform patients of the requirement to be revaccinated according to current ACIP recommendations for meningococcal infection while on BKEMV therapy *[see Warnings and Precautions (5.1)]*.

Inform patients that vaccination may not prevent serious meningococcal infection and to seek immediate medical attention if the following signs or symptoms occur *[see Warnings and Precautions (5.1)]*:

- fever
- fever and a rash
- fever with high heart rate
- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that they will be given a Patient Safety Card for BKEMV that they should carry with them at all times during and for 3 months following treatment with BKEMV. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

BKEMV REMS

BKEMV is available only through a restricted program called BKEMV REMS *[see Warnings and Precautions (5.2)]*.

Inform the patient of the following notable requirements:

- Patients must receive counseling about the risk of serious meningococcal infections.
- Patients must receive written educational materials about this risk.
- Patients must be instructed to carry the Patient Safety Card with them at all times during and for 3 months following treatment with BKEMV.
- Patients must be instructed to complete or update meningococcal vaccines for serogroups A, C, W, Y and B per ACIP recommendations as directed by the prescriber prior to treatment with BKEMV.
- Patients must receive antibiotics as directed by the prescriber if they are not up to date with meningococcal vaccines and have to start BKEMV right away.

Other Infections

Counsel patients about gonorrhea prevention and advise regular testing for patients at-risk.

Inform patients that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria.

Aspergillus infections have occurred in immunocompromised and neutropenic patients.

Inform parents or caregivers of children receiving BKEMV for the treatment of aHUS that their child should be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to current medical guidelines.

Infusion-Related Reactions

Advise patients that administration of BKEMV may result in infusion-related reactions.

Discontinuation

Inform patients with PNH that they may develop serious hemolysis due to PNH when BKEMV is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following BKEMV discontinuation.

Inform patients with aHUS that there is a potential for TMA complications due to aHUS when BKEMV is discontinued and that they will be monitored by their healthcare professional for at least 12 weeks following BKEMV discontinuation. Inform patients who discontinue BKEMV to keep the Patient Safety Card with them for three months after the last BKEMV dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of BKEMV.

AMGEN

BKEMV™ (eculizumab-aeeb)

Manufactured by:
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One Amgen Center Drive
Thousand Oaks, CA 91320-1799

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MEDICATION GUIDE

BKEMV™ (bee-KEM-vee)
(eculizumab-aeeb)
injection, for intravenous use

What is the most important information I should know about BKEMV?

BKEMV is a medicine that affects your immune system. BKEMV may lower the ability of your immune system to fight infections.

- **BKEMV increases your chance of getting serious meningococcal infections caused by *Neisseria meningitidis* bacteria. Meningococcal infections may quickly become life-threatening or cause death if not recognized and treated early.**
  - You must complete or update your meningococcal vaccine(s) at least 2 weeks before your first dose of BKEMV.
  - If you have not completed your meningococcal vaccines and BKEMV must be started right away, you should receive the required vaccine(s) as soon as possible.
  - If you have not been vaccinated and BKEMV must be started right away, you should also receive antibiotics to take for as long as your healthcare provider tells you.
  - If you had a meningococcal vaccine in the past, you might need additional vaccines before starting BKEMV. Your healthcare provider will decide if you need additional meningococcal vaccines.
  - Meningococcal vaccines do not prevent all meningococcal infections. **Call your healthcare provider or get emergency medical care right away if you get any of these signs and symptoms of a serious meningococcal infection:**
    - fever
    - fever with high heart rate
    - headache and fever
    - confusion
    - muscle aches with flu-like symptoms
    - fever and a rash
    - headache with nausea or vomiting
    - headache with a stiff neck or stiff back
    - eyes sensitive to light

Your healthcare provider will give you a Patient Safety Card about the risk of serious meningococcal infection. Carry it with you at all times during treatment and for 3 months after your last dose of BKEMV. Your risk of meningococcal infection may continue for several weeks after your last dose of BKEMV. It is important to show this card to any healthcare provider who treats you. This will help them diagnose and treat you quickly.

BKEMV is only available through a program called the BKEMV Risk Evaluation and Mitigation Strategy (REMS). Before you can receive BKEMV, your healthcare provider must:

- enroll in the BKEMV REMS program
- counsel you about the risk of serious meningococcal infections
- give you information about the signs and symptoms of serious meningococcal infection
- make sure that you are vaccinated against serious infections caused by meningococcal bacteria and that you receive antibiotics if you need to start BKEMV right away and you are not up to date on your vaccines.
- give you a **Patient Safety Card** about your risk of meningococcal infection, as discussed above

BKEMV may also increase the risk of other types of serious infections caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae***.**

- If your child is treated with BKEMV, your child should receive vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae type b* (Hib).
- Certain people may be at risk of serious infections with gonorrhea. Talk to your healthcare provider about whether you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing.
- Certain fungal infections (aspergillus) may also happen if you take BKEMV and have a weak immune system or a low white blood cell count.

For more information about side effects, see "**What are the possible side effects of BKEMV?**"

What is BKEMV?

BKEMV is a prescription medicine used to treat:

- people with paroxysmal nocturnal hemoglobinuria (PNH).
- people with atypical hemolytic uremic syndrome (aHUS).
  BKEMV is not for use in treating people with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive.

It is not known if BKEMV is safe and effective in children with PNH, or gMG.

Who should not receive BKEMV?

Do not receive BKEMV if you have a serious meningococcal infection when you are starting BKEMV treatment.

Before you receive BKEMV, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection or fever.
- are pregnant or plan to become pregnant. It is not known if BKEMV will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if BKEMV passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. BKEMV and other medicines can affect each other causing side effects.

Know the medications you take and the vaccines you receive. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I receive BKEMV?

- Your healthcare provider will give you BKEMV into your vein through an intravenous (IV) line usually over 35 minutes in adults and 1 to 4 hours in children.
- Adults will usually receive a BKEMV infusion:
  - weekly for 5 weeks, then
  - every 2 weeks.
- Children less than 18 years of age, your healthcare provider will decide how often you will receive BKEMV depending on your age and body weight.
- After each infusion, you should be monitored for at least 1 hour for infusion-related reactions. See **"What are the possible side effects of BKEMV?"** If you have an infusion-related reaction during your BKEMV infusion, your healthcare provider may decide to give BKEMV more slowly or stop your infusion.
- If you miss a BKEMV infusion, call your healthcare provider right away.
- **If you have PNH, your healthcare provider will need to monitor you closely for at least 8 weeks after stopping BKEMV. Stopping treatment with BKEMV may cause breakdown of your red blood cells due to PNH.**

  Symptoms or problems that can happen due to red blood cell breakdown include:

  - drop in the number of your red blood cell count
  - kidney problems
  - drop in your platelet counts
  - blood clots
  - confusion
  - difficulty breathing
  - chest pain

- **If you have aHUS, your healthcare provider will need to monitor you closely for at least 12 weeks after stopping BKEMV for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

  Symptoms or problems that can happen with abnormal clotting may include:

  - stroke
  - difficulty breathing
  - confusion
  - kidney problems
  - seizure
  - swelling in arms or legs
  - chest pain (angina)
  - a drop in your platelet count

What are the possible side effects of BKEMV?

BKEMV can cause serious side effects including:

- See **"What is the most important information I should know about BKEMV?"**
- **Serious infusion-related reactions.** Serious infusion-related reactions can happen during your BKEMV infusion. Tell your healthcare provider or nurse right away if you get any of these symptoms during your BKEMV infusion:
  - chest pain
  - trouble breathing or shortness of breath
  - swelling of your face, tongue, or throat
  - feel faint or pass out

If you have an infusion-related reaction to BKEMV, your healthcare provider may need to infuse BKEMV more slowly, or stop BKEMV. See **"How will I receive BKEMV?"**

The most common side effects in people with PNH treated with BKEMV include:

- headache
- pain or swelling of your nose or throat (nasopharyngitis)
- back pain
- nausea

The most common side effects in people with aHUS treated with BKEMV include:

- headache
- diarrhea
- high blood pressure (hypertension)
- common cold (upper respiratory infection)
- stomach-area (abdominal pain)
- vomiting
- pain or swelling of your nose or throat (nasopharyngitis)
- low red blood cell count (anemia)
- cough
- swelling of legs or feet (peripheral edema)
- nausea
- urinary tract infections
- fever

The most common side effects in people with gMG treated with BKEMV include:

- muscle and joint (musculoskeletal) pain

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of BKEMV. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BKEMV.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about BKEMV that is written for health professionals.

What are the ingredients in BKEMV?

Active ingredient: eculizumab-aeeb

Inactive ingredients: sorbitol (E420), acetic acid, polysorbate 80 (vegetable origin), edetate disodium (EDTA), sodium hydroxide may be added to adjust pH, and Water for Injection, USP.

AMGEN

BKEMV™ (eculizumab-aeeb)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 U.S.A.

U.S. License Number 1080

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This Medication Guide has been approved by the U.S. Food and Drug Administration Revised 10/2024