PDL DRUG REVIEW

Proprietary Name: Empaveli®
Common Name: pegcetacoplan
PDL Category: Hematological- Monoclonal Antibody

Comparable Products	Preferred Drug List Status
Soliris	Medical Coverage
Ultomiris	Medical Coverage

Summary

Pharmacology/Usage: Pegcetacoplan, the active ingredient of Empaveli®, is a complement inhibitor. It binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In paroxysmal nocturnal hemoglobinuria, extravascular hemolysis (EVH) is facilitated by C3b opsonization while intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH.

Indication: For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

There is no pregnancy category for this medication; however, the risk summary indicates that there are not sufficient data on use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH in pregnancy. The use of Empaveli® may be considered following an assessment of the risks and benefits. Clinical considerations include 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. Empaveli® may cause embryo-fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to treatment with Empaveli®. Advise female patients of reproductive potential to use effective contraception during treatment and for 40 days after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Injection: 1,080mg/20ml (54mg/ml) solution in a single-dose vial. Vials should be refrigerated but prior to use allow Empaveli® to reach room temperature for about 30 minutes.

Recommended Dosage: Vaccinate patients against encapsulated bacteria, including *Streptococcus pneumonia*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to initiation of Empaveli® per current Advisory Committee on Immunization Practices (ACIP) guidelines.

Provide 2 weeks of antibacterial drug prophylaxis to patients if Empaveli® must be initiated immediately and vaccines are administered less than 2 weeks before starting therapy with Empaveli®.

The recommended dose is 1,080mg by SC infusion twice weekly via a commercially available infusion pump with a reservoir of at least 20ml. Empaveli® is intended for use under the guidance of a healthcare professional. After proper training in SC infusion, a patient may self-administer, or the patient's caregiver may administer Empaveli®, if

a healthcare provider determines that it is appropriate. Rotate the infusion sites (i.e., abdomen, thighs, hips, upper arms) from one infusion to the next. Do not infuse where the skin is tender, bruised, red, or hard. If multi-infusion sets are needed, ensure the infusion sites are at least 3 inches apart. The typical infusion time is about 30 minutes (if using 2 infusion sites) or about 60 minutes (if using one infusion site).

With dose adjustments, for lactate dehydrogenase (LDH) levels greater than 2 times the upper limit of normal (ULN), adjust the dosing regimen to 1,080mg every 3 days. In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

There are recommendations regarding the dosage for patients switching to Empaveli® from C5 inhibitors. To reduce the risk of hemolysis with abrupt treatment discontinuation:

- For patients switching from eculizumab (under the brand name Soliris®), initiate Empaveli® while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with Empaveli®.
- For patients switching from ravulizumab (under the brand name Ultomiris®), initiate Empaveli® no more than 4 weeks after the last dose of ravulizumab.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: Empaveli® has a box warning regarding serious infections caused by encapsulated bacteria. Meningococcal infections may occur in patients treated with Empaveli® and may become rapidly life threatening or fatal if not recognized and treated early. Use of Empaveli® may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumonia*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B. Thus, comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients with altered immunocompetence associated with complement deficiencies. Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of Empaveli® unless the risks of delaying therapy with Empaveli® outweigh the risk of developing a serious infection. Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.

Due to the risk of serious infections, Empaveli® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Empaveli® REMS, prescribers must enroll in the program. Enrollment and additional information are available by calling 1-888-343-7073 or visiting www.empavelirems.com.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Empaveli®) minus reported % incidence for eculizumab. Please note that an incidence of 0% means the incidence was the same as or less than the comparator.* The most frequently reported adverse events included injection-site reaction (34%), fatigue (0%), chest pain (4%), infections (3%), respiratory tract infection (2%), viral infection (4%), diarrhea (19%), abdominal pain (10%), back pain (0%), headache (0%), and systemic hypertension (4%). Clinically relevant adverse reactions in less than 5% of patients include intestinal ischemia, biliary sepsis, and hypersensitivity pneumonitis.

Systemic hypersensitivity reactions have occurred in patients treated with Empaveli®. If a severe hypersensitivity reaction occurs, discontinue Empaveli® infusion immediately, start appropriate treatment, per standard of care, and monitor until signs and symptoms are resolved.

After discontinuing treatment with Empaveli®, closely monitor for signs and symptoms of hemolysis. Monitor any patient who discontinues Empaveli® for at least 8 weeks to detect hemolysis and other reactions. If hemolysis, including elevated LDH, occurs after discontinuation of Empaveli®, consider restarting treatment with Empaveli®.

Contraindications: In patients:

- With hypersensitivity to pegcetacoplan or to any of the excipients
- Who are not currently vaccinated against certain encapsulated bacteria, unless the risks of delaying Empaveli® treatment outweigh the risks of developing a bacterial infection with an encapsulated organism
- With unresolved serious infection caused by encapsulated bacteria including *Streptococcus pneumonia*, *Neisseria meningitidis*, and *Haemophilus influenzae*

Manufacturer: Apellis Pharmaceuticals, Inc

Analysis: The safety and efficacy of Empaveli® in patients with PNH were assessed in a randomized, open-label, active comparator-controlled, 16-week, phase 3 study that included patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels less than 10.5g/dL (N=80). Eligible patients entered a 4-week run-in period during which they received Empaveli® 1,080mg SC twice weekly in addition to their current dose of eculizumab. Patients were then randomized to receive either 1,080mg Empaveli® twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period (RCP). If required, the dose of Empaveli® could be adjusted to 1,080mg every 3 days. Following completion of the RCP, all entered a 32-week open-label period and received monotherapy with Empaveli®. All patients who completed the 48-week period were eligible to enroll in a separate long-term extension study.

Patients were vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B, either within 2 years prior to day 1 or within 2 weeks after starting treatment with Empaveli®. Patients vaccinated after initiation of treatment with Empaveli® received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. Also, prophylactic antibiotic therapy was administered at the discretion of the investigator per local treatment guidelines for patients with PNH receiving treatment with a complement inhibitor.

Patients were randomized to receive treatment with Empaveli® (N=41) or eculizumab (N=39). The baseline mean total PNH RBC clone sizes (Type III) were 47% for Empaveli® and 50% for eculizumab. In addition, 29% and 23% of patients had a history of major adverse vascular events while 37% and 26% had a history of thrombosis for patients receiving Empaveli® or eculizumab, respectively. Within 28 days prior to the first-dose of Empaveli® or eculizumab, respectively, 34% and 31% of subjects used anti-thrombotic agents (antiplatelets and/or anticoagulants); and, during the study, 37% and 36% of subjects on Empaveli® and eculizumab, respectively, used anti-thrombotic agents. A total of 38 in the Empaveli® group and 39 in the eculizumab group completed the 16-week RCP and continued into the 32 week open-label period. The mean age of the Empaveli® group was 50.2 years while it was 47.3 years with the eculizumab group. Furthermore 65.9% of the Empaveli® group were female and 58.5% were white, while in the eculizumab group 56.4% were female and 64.1% were white.

The efficacy of Empaveli® was based on the change from baseline to week 16 (during RCP) in hemoglobin level. Baseline was defined as the average of measurements recorded prior to taking the first dose of Empaveli®. Supportive efficacy data included transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the RCP, and change from baseline to week 16 in absolute reticulocyte count (ARC). Results suggested that Empaveli® was superior to eculizumab for the change from baseline in hemoglobin level at week 16 ($p<0.0001$). The adjusted mean change from baseline in hemoglobin level was 2.37g/dL in the Empaveli® group vs -1.47g/dL in the eculizumab group, demonstrating an adjusted mean increase of 3.84g/dL with Empaveli® compared to eculizumab at week 16.

Non-inferiority was demonstrated in the endpoints of transfusion avoidance and change from baseline in ARC. The adjusted means and treatment differences can be seen in the table below, which was adapted from the prescribing information.

	Empaveli® (N=41)	Eculizumab (N=39)	Difference
Transfusion avoidance, n (%)	35 (85%)	6 (15%)	63%
Chane from baseline in ARC (10^9 cells/L), LS mean	-136	28	-164

The results of the controlled trial of Empaveli® in patients with PNH are supported by 2 uncontrolled studies in patients with PNH who were not receiving a complement inhibitor. These studies enrolled a total of 24 patients with PNH who had a PNH clone size of at least 10%, an LDH at least 2 times the upper limit of normal, and at least 1 transfusion in the 12 months prior to enrollment. In both studies, the treatment duration was about 1 year. Increases in hemoglobin were observed in both studies.

Place in Therapy: Empaveli®, a complement inhibitor given as SC infusion, is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). While it is intended for use under the guidance of a healthcare professional, after proper training in subcutaneous infusion, a patient may self-administer Empaveli®, or the patient's caregiver may administer Empaveli® if a healthcare provider determines that it is appropriate. Due to the risk of serious infections, Empaveli® is available only through a restricted program under a REMS, called the Empaveli® REMS. It is recommended to vaccinate patients against encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to initiation of Empaveli® therapy per current ACIP guidelines. In an open-label, active-comparator clinical study comparing Empaveli® with eculizumab, Empaveli® was superior to eculizumab for the change from baseline in hemoglobin level at week 16, the primary outcome. Non-inferiority of Empaveli® was demonstrated in the endpoints of transfusion avoidance and change from baseline in absolute reticulocyte count (ARC).

There is some evidence at this time to suggest that Empaveli® may be more effective than eculizumab for the primary outcome of change from baseline in hemoglobin level at 16 weeks in a phase 3 study, but non-inferiority was demonstrated for the endpoints of transfusion avoidance and change from baseline in ARC. It is therefore recommended that Empaveli® remain non-preferred in order to confirm all manufacturer prescribing requirements are met, including but not limited to the appropriate diagnosis, clinical parameters for use, training and no overlap with comparable products available under the medical benefit.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Empaveli [package insert]. Waltham, MA: Apellis Pharmaceuticals; 2021.