NEW DRUG APPROVAL

Brand Name	Empaveli™
Generic Name	pegcetacoplan
Drug Manufacturer	Apellis Pharmaceuticals, Inc

New Drug Approval

FDA Approval Date: May 14, 2021
Review Designation: Priority; Orphan
Type of Review: Type 1 - New Molecular Entity, New Drug Application (NDA): 215014
Dispensing Restrictions: Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease that presents clinically with a variety of symptoms, the most prevalent of which are hemolytic anemia, hemoglobinuria, and somatic symptoms including fatigue and shortness of breath. Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, even bone marrow failure. The condition is genetic, with the mutations occurring on the X linked gene.

PNH is rare, with occurrence estimated as high as 15.9 individuals per million worldwide. Some authors indicate that this number is probably low as the disease remains undiagnosed in individuals with limited symptomatology, or with comorbid conditions that obscure the PNH diagnosis. Typically, most patients fall in the age range of 30 years to 40 years. Children can be affected by PNH as well, but it is uncommon. For instance, according to an analysis of 1610 patients registered in the International PNH Registry in 2012, the median age of all registered patients was 42 years, with the disease duration of 4.6 years. The age range of patients in the registry was 3 to 99 years.

Although the condition is due to an X-linked chromosome mutation, women are affected at a slightly higher rate than men. This is because the acquired defect occurs in somatic, or clone, hematopoietic stem cells, rather than germ cells. The phenotype can be created due to a single somatic mutation. Men only have one X chromosome, and women only express a single X chromosome due to lyonization, or inactivation of the duplicate X chromosome. Therefore, once the mutation occurs, the cell line perpetuates the abnormality until clonal superiority is achieved, and the phenotype is expressed.

Patients affected by PNH in the US demonstrate differences in complications according to ethnic groups. African Americans with PNH have a 73% rate of thromboembolism (TE) and Latin Americans, about 50%. White race and Asian Americans have a 36% rate of TE complications. They have also demonstrated bone marrow failure to vary with ethnicity or geography. It is more common in residents of Asia, the Pacific Islands, and Latin America. The reasons for these variations are not clear.

Efficacy

The approval of Empaveli™was based on the Phase 3 PEGASUS study (APL2-302; NCT03500549). This was a multicenter, randomized, head-to-head study in 80 adults with PNH comparing Empaveli™ to Soliris.

Table 1. PEGASUS (APL-2-302; NCT03500549) Study Design Summary

Study	• Randomized, open-label, active comparator-controlled trial

Population	**Baseline Demographics for Study APL2-302**

Parameter	Pegcetacoplan (n = 41)	Eculizumab (n = 39)
Mean age (years)	50.2	47.3
Mean hemoglobin level (g/dL)	8.7	8.7
Mean absolute reticulocyte count (10^9 cells/L)	218	216
Mean LDH level	257.5	308.6
Number (%) of transfusions in the last 12 months prior to Day −28		
<4	20 (48.8)	16 (41.0)
≥4	21 (51.2)	23 (59.0)

Interventions	• Trial consisted of 3 parts: ○ **Run-in** (4 weeks): all patients continued to receive current dose of eculizumab with the addition of twice-weekly pegcetacoplan 1080 mg (patients self-administered) ○ **Randomized, controlled** (16 weeks): patients received pegcetacoplan 1080 mg twice weekly (n = 41) OR eculizumab (n = 39) ○ **Open-label** (32 weeks): all patients who completed the randomized controlled period (n = 77) received open-label pegcetacoplan
Endpoints	• **Primary endpoint**: change from baseline to Week 16 in hemoglobin level during the randomized, controlled period • **Key secondary endpoints**: proportion of patients who did not require a transfusion, change from baseline to Week 16 in absolute reticulocyte count, LDH level, and score on the FACIT-F scale (scores range from 0 to 52, with higher scores indicating less fatigue)

FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LDH, lactate dehydrogenase

Table 2. Additional Efficacy Results

	Empaveli (n = 41)	Eculizumab (n = 39)	Difference (95% CI)
Transfusion avoidance, n (%)	35 (85%)	6 (15%)	63% (48%, 77%)
Change from baseline in absolute reticulocyte count (10^9 cells/L), LS mean (SE)	−136 (6.5)	28 (11.9)	−164 (−189.9, −137.3)

Abbreviations: LS, least square; SE, standard error

Safety

ADVERSE EVENTS

Most common adverse reactions in patients with PNH (incidence ≥10%) were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue.

WARNINGS & PRECAUTIONS

Use caution when administering Empaveli™ to patients with:

- Serious infections caused by encapsulated bacteria.
- Infusion-Related Reactions: Monitor patients for infusion-related reactions and institute appropriate medical management as needed.
- Interference with Laboratory Tests: Use of silica reagents in coagulation panels may result in artificially prolonged activated partial thromboplastin time (aPTT).

CONTRAINDICATIONS

Empaveli™ is contraindicated in:

- Patients with hypersensitivity to pegcetacoplan or any of the excipients.
- Patients who are not currently vaccinated against certain encapsulated bacteria unless the risks of delaying Empaveli™ treatment outweigh the risks of developing a serious bacterial infection with an encapsulated organism.
- Patients with unresolved serious infection caused by encapsulated bacteria.

Clinical Pharmacology

MECHANISMS OF ACTION

Pegcetacoplan 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 PNH, 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.

Dose & Administration

ADULTS

1,080 mg via subcutaneous infusion twice weekly.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

HEPATIC IMPAIRMENT

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

- Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial.