



Positive Quality Intervention: Pegcetacoplan (Empaveli®) Use in Paroxysmal Nocturnal Hemoglobinuria

Description: Pegcetacoplan is a proximal complement inhibitor indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). PNH is a rare, acquired condition caused by dysregulation of the complement pathway leading to hemolysis, fatigue, thrombosis, organ dysfunction and bone marrow hypocellularity. This PQI will focus on the role of pegcetacoplan in the management of PNH.

Background: Pegcetacoplan is the first C3 inhibitor approved for PNH. While C5 inhibitors only inhibit intravascular hemolysis, pegcetacoplan is a pegylated peptide that targets the proximal complement protein C3 and can inhibit both intravascular and extravascular hemolysis, providing an option for patients with refractory or breakthrough disease.¹ The PRINCE trial enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrollment and with hemoglobin levels less than the lower limit of normal. Eligible patients were randomized in a 2:1 ratio to receive pegcetacoplan or supportive care through the duration of the 26-week treatment period. A total of 53 patients were randomized, 35 to pegcetacoplan and 18 to the control arm. Hemoglobin stabilization was achieved by 85.7% (n=30) of PEG-treated patients and 0.0% of SOC patients through Week 26 (p<0.0001). Pegcetacoplan patients demonstrated superior reductions in mean LDH levels from baseline to Week 26 compared to the supportive care arm.² The PEGASUS trial was a 48-week, phase 3, randomized, multicenter, open-label, active-comparator-controlled trial which enrolled 80 adult patients with PNH who had hemoglobin levels of less than 10.5 g/dL despite 3 months of eculizumab.³ Patients received a 4-week run-in with both pegcetacoplan and eculizumab then were randomized to continue either drug as monotherapy for 16 weeks. All patients were allowed to continue pegcetacoplan (open-label) for an additional 32 weeks. The primary endpoint was change in hemoglobin from baseline to week 16. The results showed a mean change of 2.37 g/dL in the pegcetacoplan (n=41) group compared to -1.47 g/dL in the eculizumab (n=39) group (mean difference: 3.84 g/dL, P<0.001). The change was seen as early as week 2. There were also improvements in Functional Assessment of Chronic Illness Therapy–Fatigue scores (mean difference 11.9 points), proportion of patients transfusion-free (85% v 15%), and lactate dehydrogenase (LDH) normalization (71% v 15%) with pegcetacoplan. Adverse events occurred in 88% of pegcetacoplan patients compared to 87% of subjects in the eculizumab arm. The most common adverse events that occurred during treatment in the pegcetacoplan and eculizumab groups were injection site reactions (37% v 3%), diarrhea (22% vs. 3%), breakthrough hemolysis (10% v 23%), headache (7% v 23%), and fatigue (5% v 15%). There were no cases of meningitis in either group. Pegcetacoplan was also shown to be effective and well tolerated as first line treatment in the complement naïve population.⁴

PQI Process: Upon order of pegcetacoplan¹

- Confirm diagnosis for PNH and assess patient’s need for treatment and prior therapies received
- Assess the patient’s medical history for contraindications to pegcetacoplan
 - Hypersensitivity to pegcetacoplan or any component of formulation
 - Black Box Warning: Vaccinate patients against encapsulated bacteria at least 2 weeks prior to administering the first dose of pegcetacoplan unless the risks of delaying therapy outweigh the risks of developing a serious infection
 - Contraindicated in unresolved serious infection caused by encapsulated bacteria including *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*
 - If immediate pegcetacoplan administration is necessary and less than 2 weeks after vaccination, provide 2 weeks of antibacterial prophylaxis
- Evaluate pregnancy status prior to use in patients who may become pregnant

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- Verify the dose, frequency, and timing of administration (if switching from another product) are correct
 - Pegcetacoplan 1080 mg twice weekly (for LDH > 2 times ULN, adjust to 1080 mg every 3 days)
 - When switching from eculizumab, start pegcetacoplan and continue eculizumab for 4 more weeks
 - For ravulizumab, start pegcetacoplan no more than 4 weeks after last dose of ravulizumab
 - While no dose adjustments for renal or hepatic impairment are provided in the manufacturer’s labeling, no clinically significant differences in pharmacokinetics have been found in patients with reduced kidney or liver function
- Availability – only through restricted program under a Risk Evaluation and Mitigation Strategy (REMS)
 - All prescribing providers and dispensing pharmacies must be enrolled in REMS program (telephone: 1-888-343-7073 or at www.empavelirems.com)
 - Patients must be provided with REMS educational materials, be counseled about risk of serious infection caused by encapsulated bacteria (including *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*), and be vaccinated against such bacteria ≥ 2 weeks prior to starting pegcetacoplan according to current ACIP guidelines
 - Patients started urgently should be given 2 weeks of antibacterial drug prophylaxis
- Monitoring - hemoglobin, LDH at baseline, periodically, and twice weekly for ≥ 4 weeks after dose change
 - Avoid silica reagents in coagulation panels as drug may artificially prolong aPTT levels
 - Monitor for signs/symptoms of hemolysis for ≥ 8 weeks after last dose

Patient-Centered Activities:

- Counsel patients to watch for/report:
 - Signs/symptoms of severe infections (fever, chills, rash, shortness of breath, stiff neck/back, headache, high heart rate, light sensitivity) while on the drug and for 2 months after stopping
 - Serious hypersensitivity reactions (anaphylaxis, facial swelling, rash, urticaria)
 - Signs/symptoms of hemolysis (fever, weakness, dizziness, confusion, dark urine, yellowing of skin/eyes/mouth)
 - Other common adverse events (injection-site reactions, rash, diarrhea, abdominal pain, fatigue, cough, headache, joint pain)
- Educate patients on proper storage, preparation, and administration techniques per product labeling:
 - Store vials in refrigerator between 36-46°F (2-8°C) in original carton to protect from light
 - Given under the skin over 30-60 minutes (subcutaneously) via infusion pump
 - Rotate infusion sites (i.e. abdomen, thighs, hips, upper arms); if multiple sites used for same dose, keep ≥ 3 inches apart; avoid tender/bruised/red/hard skin, tattoos, scars, stretch marks
 - Upon missed dose, give as soon as possible and administer next dose at regularly scheduled time
- Carry *Patient Safety Card* about serious infection risk during treatment and for 2 months after last dose
- Advise females of reproductive age to use contraception during therapy and for 40 days after last dose
- Instruct patients to notify their provider of any new medications/supplements and stay up-to-date on vaccinations throughout the duration of therapy
- Patient Assistance: [NCODA Financial Assistance Tool](#)
 - ApellisAssist program offers disease/drug education, financial assistance, insurance support, and drug self-administration training (1-866-MY-APL-ASSIST (1-866-692-7527) or at www.empaveli.com)

References:

1. [EMPAVELI \[prescribing information\]](#). Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023.
2. Wong, Raymond S, et al. “Efficacy and Safety of Pegcetacoplan Treatment in Complement-Inhibitor Naïve Patients with Paroxysmal Nocturnal Hemoglobinuria: Results from the Phase 3 Prince Study.” *Blood*, vol. 138, no. Supplement 1, 5 Nov. 2021, pp. 606–606, <https://doi.org/10.1182/blood-2021-147493>.
3. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria (PEGASUS). *N Engl J Med*. 2021;384(11):1028-1037. doi: 10.1056/NEJMoa2029073.
4. Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria (PRINCE). *Blood Adv*. 2023;7(11): 2468–2478. doi: 10.1182/bloodadvances.2022009129.

