Pegcetacoplan (EMPAVELI)
National Drug Monograph
April 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Pegcetacoplan is a complement C3 inhibitor. For paroxysmal nocturnal hemoglobinuria (PNH), this interferes with the complement cascade that controls extravascular and intravascular hemolysis.

Indication(s) Under Review in This Document

- Paroxysmal nocturnal hemoglobinuria

Dosage Form(s) Under Review

- Single-dose vial for injection: 1080mg/20mL
- Dose in PNH is 1080mg by subcutaneous infusion twice weekly. Infusion should be 30 minutes if using two infusion sides or 60 minutes if using one infusion site.

REMS

- Empaveli REMS is in place for safe prescribing of pegcetacoplan. It requires that prescribers enroll in the REMS program. Providers must counsel patients on the risk of serious infection, provide the patient with REMS educational materials, and ensure that patients are vaccinated against encapsulated bacteria (like Streptococcus pneumoniae, Neisseria meningitidis, and Hemophilus influenzae).
- The REMS program also requires pharmacies that dispense pegcetacoplan be REMS registered. Due to the Empaveli REMS administrative requirements, including the need to submit daily data files to the REMS coordinator, it is recommended that sites use the program's specialty pharmacy to dispense the product.

Clinical Evidence Summary

Efficacy Considerations

There were two phase III trials to support the efficacy and approval of pegcetacoplan in PNH: PRINCE and PEGASUS. Both were open label trials, but the study populations and treatment arms differed. PEGASUS enrolled patients previously on eculizumab (a complement C5 inhibitor) and randomized

them to switch to pegcetacoplan or stay on eculizumab. On the other hand, PRINCE enrolled patients who were complement inhibitor naïve and randomized them to either continue with supportive care (blood transfusions, steroids, supplements) or initiate pegcetacoplan.

PEGASUS was an open label active comparator trial[1]. Patients enrolled had been on a stable dose of eculizumab for at least 3 months and a hemoglobin level of less than 10.5 g/dL. There was a 4-week run-in phase where all patients received both eculizumab and pegcetacoplan. Then patients were randomized to either pegcetacoplan monotherapy or eculizumab monotherapy for 16 weeks. The randomization was stratified by number of transfusions the patient had received in the 12 months prior and the platelet count at baseline. Of note, this resulted in the pegcetacoplan group being earlier in disease (average 6 years since diagnosis vs. 9.7 years), having a longer history on eculizumab (average 4.4 years vs. 3.4 years), and a higher baseline eculizumab dosing (37% of patients on greater than 900mg Q2weeks vs. 23% of patients) than the eculizumab group. After the 16 weeks of monotherapy, all patients switched to pegcetacoplan for 32 weeks. The primary endpoint was the change in hemoglobin level from baseline to week 16.

Pegcetacoplan was determined to be superior to eculizumab in the primary endpoint and noninferior to eculizumab on freedom from transfusion and reticulocyte count change (See Table 1). Though fatigue improvement was seen in the week 16 data of PEGASUS, it could not be evaluated for statistical significance due to the hierarchical testing model of the secondary endpoints. A post-hoc analysis reported on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) rating scales in PEGASUS[2]. Results showed that patients on pegcetacoplan experienced the greatest improvement on physical functioning, role functioning, social functioning, fatigue, and dyspnea.

In the 32-week pegcetacoplan continuation period where patients either remained on pegcetacoplan or were switched from eculizumab to pegcetacoplan, there was no significant change in hemoglobin in the pegcetacoplan to pegcetacoplan group, but the eculizumab to pegcetacoplan group experienced a significant increase in hemoglobin (from 8.58 g/dL at week 16 to 11.57 g/dL at week 48)[3]. The between group difference in hemoglobin at week 48 was not significant. Similar trends were seen with lactate dehydrogenase (LDH), reticulocyte counts, and FACIT-F scores.

PRINCE was a 26-week open label trial of pegcetacoplan versus supportive care (ie no disease modifying therapy)[4]. Patients enrolled were complement inhibitor naïve. Similar to PEGASUS, the randomization was stratified by the number of transfusions received in the 12 months prior to screening. Supportive care group patients could escape to the pegcetacoplan group if their hemoglobin dropped by 2 or more g/dL or if they had a qualifying thromboembolic event. The coprimary endpoints were hemoglobin stabilization (defined as patients who had no more than 1 g/dL increase in hemoglobin from baseline to week 26) and change in LDH level from baseline to week 26. Over the course of the study, 11 of the 18 patients in the supportive care group “escaped” to pegcetacoplan. For the purposes of efficacy data these “escape” patients were still considered as a part of the control group and would be marked as not having a hemoglobin response. For safety analysis, the “escape”

patients were included in the pegcetacoplan group. A significantly higher number of patients originally randomized to the pegcetacoplan group experienced hemoglobin response (see Table 1). The pegcetacoplan group also had a statistically significant treatment difference in LDH lowering.

A matched indirect comparison study exists to attempt to examine pegcetacoplan efficacy vs complement C5 inhibitor efficacy in complement inhibitor naïve patients[5]. This study used the pegcetacoplan group from PRINCE and the results from one ravulizumab's phase III studies that compared ravulizumab to eculizumab. Weighting was used to try and account for differences in baseline characteristics between these two studies. It should be noted that there were also some slight differences in definitions of endpoints that could affect comparative analysis. However, after weighting, pegcetacoplan was found to have statistically significant improvement in LDH and hemoglobin vs. the complement C5 inhibitors. Pegcetacoplan was also associated with significantly less transfusions than the complement C5 inhibitors. This does seem to follow the trend of results in PEGASUS (though patients in that study had all been on eculizumab prior to start of the study). Pegcetacoplan was associated with greater increases on the general health status score on the EORTC QLQ-C30, but there were no other significant differences between pegcetacoplan and the complement C5 inhibitors on any other quality of life outcomes.

Table 1: Efficacy results from phase III trials

<table>
<tr><th>Study</th><th>Design</th><th>Results</th></tr>
<tr><td>PEGASUS[1]
Phase III trial
Open label
N = 80</td><td>All patients were on eculizumab with a hemoglobin level less than 10.5 g/dL at the time of enrollment.

Trial consisted of three parts:
1) 4-week run-in where patients took eculizumab and pegcetacoplan
2) 16-week randomized controlled period where patients were on either pegcetacoplan or eculizumab
3) 32-week period that all patients were on pegcetacoplan</td><td>All results described as least-squares mean change from baseline to week 16 except where indicated:

<u>Primary:</u>
<table>
<tr><th></th><th>Pegcetacoplan</th><th>Eculizumab</th><th>Pegcetacoplan TD (95% CI)</th><th>p value</th></tr>
<tr><td>Δ Hemoglobin</td><td>2.4 ± 0.4</td><td>-1.5 ± 0.7</td><td>3.8
(2.3 to 5.3)</td><td>p<0.0001
Superiority</td></tr>
</table>
<u>Secondary:</u>
<table>
<tr><th></th><th>Pegcetacoplan</th><th>Eculizumab</th><th>Pegcetacoplan TD (95% CI)</th><th>p value</th></tr>
<tr><td>Freedom from transfusion no.(%)</td><td>35 (85)</td><td>6 (15)</td><td>63
(48 to 77)</td><td>p<0.0001
Noninferior</td></tr>
<tr><td>Δ Reticulocyte</td><td>-136 ± 6.5</td><td>28 ± 11.9</td><td>-164
(-189.9 to -137.3)</td><td>p<0.0001
Noninferior</td></tr>
<tr><td>Δ LDH</td><td>-15 ± 42.7</td><td>-10 ± 71</td><td>-5
(-181.3 to 172)</td><td>p=0.96</td></tr>
<tr><td>Δ FACIT-F</td><td>9.2 ±1.6</td><td>-2.7 ± 2.8</td><td>11.9
(5.5 to 18.3)</td><td>n/a</td></tr>
</table></td></tr>
<tr><td>PRINCE[4]
Phase III
Open Label
N = 53</td><td>All patients were complement C5 inhibitor naïve at the time of enrollment.</td><td>All results described as least-squares mean change from baseline to week 26 except where indicated:
<u>Primary:</u>
<table>
<tr><th></th><th>Pegcetacoplan</th><th>Supportive Care</th><th>TD (95% CI)</th><th>p value</th></tr>
<tr><td>Hemoglobin Response n(%)</td><td>25 (71.4%)</td><td>1 (5.6)</td><td>54.1
(33.9 to 74.3)</td><td>p<0.001</td></tr>
</table></td></tr>
</table>

Secondary:

	Pegcetacoplan	Supportive Care	TD (95% CI)	p value
Δ Reticulocyte	-123.3 (9.2)	-19.4 (25.2)	63 (48 to 77)	p=0.002
Δ Hemoglobin	2.9 (0.4)	0.3 (0.8)	2.7 (1 to 4.4)	p=0.0019
Transfusion Avoidance *n(%)*	32 (91.4)	1 (5.6)	72.4 (55.8 to 89)	p<0.0001
Δ FACIT-F	7.8 (1.2)	3.3 (2.1)	4.5 (-0.2 to 9.2)	p=0.061
EORTC QLQ-C30	18.9 (2.9)	-2.9 (5.7)	21.8 (9.4 to 34.2)	n/a
Reticulocyte normalization *n(%)*	21 (60)	1 (5.6)	46.4 (25.3 to 67.5)	n/a
Clinically meaningful FACIT-Fatigue score *n(%)*	21 (60)	2 (11.1)	48.9 (27.1 to 70.7)	n/a
Hemoglobin normalization *n(%)*	16 (45.7)	0 (0)	36.5 (16.5 to 56.4)	n/a
LDH normalization *n(%)*	23 (65.7)	0 (0)	55.9 (36.8 to 75)	n/a

Safety Considerations[6]

Safety Results from Clinical Trials:
In randomized period of PEGAUS, there was a similar adverse event incidence between the pegcetacoplan and eculizumab groups[1]. The most common adverse reactions that occurred in 10% or more of patients were injection site reactions, diarrhea, abdominal pain, and breakthrough hemolysis. In the 32-week period that all patients were on pegcetacoplan, additional adverse reactions that occurred in at least 10% of patients included nasopharyngitis, fatigue, headache, cough, urinary tract infection, and oral herpes[2].

In PRINCE 28.3% of patients in the pegcetacoplan group had an adverse reaction that was determined to be related to the treatment. Adverse reactions that occurred in 10% or more of the pegcetacoplan treatment patients were hypokalemia, dizziness, injection site reactions, infections, and hypersensitivity[4].

- **Boxed warnings:** Serious infections caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B. It is recommended to adhere to ACIP recommendations for vaccinations in people with complement deficiencies. Vaccination should occur at least 2 weeks before administering the first dose of pegcetacoplan.

- **EMPAVELI REMS**
  - Empaveli REMS is in place for safe prescribing of pegcetacoplan. It requires that prescribers enroll in the REMS program. Providers must counsel patients on the risk of serious infection, provide the patient with REMS educational materials, and ensure that patients are vaccinated against encapsulated bacteria (like Streptococcus pneumoniae, Neisseria meningitidis, and Hemophilus influenzae).
  - The REMS program also requires pharmacies that dispense pegcetacoplan be REMS registered. Due to the Empaveli REMS administrative requirements, including the need to submit daily data files to the REMS coordinator, it is recommended that sites use the program's specialty pharmacy to dispense the product.
- **Contraindications:** Hypersensitivity to pegcetacoplan or any component of the formulation, patients who are not currently vaccinated against encapsulated bacteria (unless the risks of delaying treatment outweigh the risk of infection), and unresolved infection caused by encapsulated bacteria.
- **Other warnings / precautions**: if signs of hemolysis occur after discontinuation, it is recommended to consider restarting pegcetacoplan treatment
- Live vaccines should not be administered to patients on pegcetacoplan
- **Serious Adverse events / Deaths / Discontinuation:** There was one death in the pegcetacoplan group of PRINCE which was related to septic shock in the context of bone marrow failure (determined unrelated to pegcetacoplan)[4]. In the entire duration of PEGASUS there were 5 serious infections of various etiologies in patients on pegcetacoplan. One of those serious infections was from COVID-19 and resulted in death[2].

Other Considerations[6]

- There is insufficient data on the drug associated risk of birth defect, miscarriage, or adverse maternal or fetal outcomes. In animal studies, a dose of 28mg/kg/day (~2.9 times the expected human exposure based on AUC) given to pregnant monkeys resulted in a significant increase in stillbirths and abortions compared to control. It is also important to note that there are risks to the mother and fetus of untreated PNH during pregnancy.
- It is not known whether pegcetacoplan is secreted in human milk and whether there is potential for absorption and harm to the infant. In animal studies, pegcetacoplan was present in the milk of lactating monkeys. It is recommended to avoid breastfeeding during treatment and up to 40 days after the last dose of pegcetacoplan.

Other Therapeutic Options

Alternative treatments for PNH are listed in table 2 below.

Table 2 Treatment Alternatives

Drug	Formulary status	Clinical Guidance
Pegcetacoplan Complement C3 inhibitor	TBD	Administered via subcutaneous infusion twice weekly. Patient can self-administer. Obtained via specialty pharmacy
Ravulizumab Complement C5 inhibitor	NF w/ CFU	Administered via IV infusion, maintenance dosing every 8 weeks. Weight based dosing.
Eculizumab Complement C5 inhibitor	NF w/ CFU	Administered via IV infusion, maintenance dosing every 2 weeks.

Projected Place in Therapy

- PNH is a rare disease affecting about 1-10 people per million[6].
- Pegcetacoplan is a complement C3 inhibitor indicated for the treatment of PNH. There are no head-to-head studies of pegcetacoplan versus other complement C5 inhibitors (like ravulizumab and eculizumab) in complement inhibitor naïve patients.
- In terms of administration, pegcetacoplan has a more frequent administration schedule with twice weekly subcutaneous infusions. This is more frequent that Q8 week infusions with ravulizumab and Q2 week infusions with eculizumab.
- The PEGASUS trial demonstrated that in patients refractory to eculizumab, pegcetacoplan may be effective.
- Though no treatment guidelines exist that define its place in therapy for PNH, the European Medical Association approved pegcetacoplan for patients who remain anemic after at least three months of complement C5 inhibitor therapy.
- Given the higher burden of administration and similar safety risks to complement C5 inhibitors, it may be reasonable to consider pegcetacoplan in patients refractory to a complement C5 inhibitor including those that experience breakthrough hemolysis.

References

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2) Cella D, Sarda SP, Hsieh R, et al. Changes in hemoglobin and clinical outcomes drive improvements in fatigue, quality of life, and physical function in patients with paroxysmal nocturnal hemoglobinuria: post hoc analyses from the phase III PEGASUS study. Annals of Hematology. 2022; 101:1905-1914.
3) De Latour RP, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PEGASUS): 48-week follow-up of a randomized, open-label, phase 3, active-comparator, controlled trial. Lancet Heamatol 2022; 9: e648-59
4) Wong R, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor naïve patients with paroxysmal nocturnal hemoglobinuria. Blood Adv. 2023 Feb 27. doi: 10.1182/bloodadvances.2022009129. online ahead of print
5) Wong R, Fishman J, Wilson K, et al. Comparative effectiveness of pegcetacoplan versus ravulizumab and eculizumab in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria: a matching-adjusted indirect comparison. Adv Ther. 2023 Feb 7. doi: 10.1007/s12325-023-02438-9. Online ahead of print.
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7) Schrezenmeier H, Muus P, Socie G, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica. 2014 May; 99(5):922-9

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