Empaveli (pegcetacoplan) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date
06-01-2024

Date of Origin
10-01-2021

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Empaveli® (pegcetacoplan) Injection for subcutaneous use	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)		1

See package insert for FDA prescribing information: *https://dailymed.nlm.nih.gov/dailymed/index.cfm*

CLINICAL RATIONALE

Paroxysmal Nocturnal Hemoglobinuria	Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening, rare, multi-systemic disease developing as a result of somatic mutation of hematopoietic stem cells, and characterized by clonal, complement-mediated intravascular hemolysis. PNH is mainly a disease of adults with a median age of onset in the thirties. High Precision Flow Cytometry is the most useful and accepted diagnostic test to confirm the diagnosis of PNH. Flow cytometry is performed by incubating the patient's peripheral blood cells with fluorescently-labeled monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI) anchored proteins, which are reduced or absent on blood cells in PNH. Since different blood cell lineages display different combinations of GPI-linked proteins, and some proteins bind to cell surfaces via both GPI-linked and GPI-independent mechanisms, it is recommended that at least two independent flow cytometry reagents be used on at least two cell lineages (e.g., RBCs and WBCs) to establish the diagnosis of PNH.(2) Lack of the complement inhibitor CD59 the red blood cells surface is mostly responsible for the clinical manifestations in PNH. These patients manifest with chronic intravascular hemolysis, paroxysmal flares of hemolysis and a propensity for thrombosis. Intravascular hemolysis leads to release of free hemoglobin (Hb) into the blood. Free hemoglobin, in turn, can cause various toxic effects, including hypercoagulability, changes in vascular tone from reduction of circulating nitric oxide and renal damage.(3) Extravascular hemolysis also occurs in patients with PNH because C3 fragments that are not destroyed by the membrane attack complex (MAC) intravascularly can accumulate on the GPI-negative red blood cell (lacking CD55) surface and these

	fragments opsonize the red blood cells, causing reticuloendothelial destruction in the liver and spleen.(3)
	The main clinical situations or diseases that should be considered in the differential diagnosis of PNH are:(3)
	• Coombs-negative hemolytic anemia (e.g., hemoglobinopathies, hereditary spherocytosis), microangiopathic hemolytic anemias, drug- or toxin-induced hemolysis/anemias, disseminated intravascular coagulation, and autoimmune hemolysis • Venous thrombosis in atypical sites, including myeloproliferative disorders; solid tumors associated with hypercoagulability; extrinsic compression of vessels, and; inherited/acquired thrombophilias • Anemia and/or other cytopenias related to bone marrow failure syndrome (e.g., aplastic anemia, MDS)
	PNH is classified into three different categories:(3)
	• Classic PNH (PNH with clinical and laboratory findings of intravascular hemolysis without any evidence of bone marrow deficiency) • PNH in the setting of another specified bone marrow disorder (evidence of hemolysis, as well as another specified bone marrow disorder [e.g., aplastic anemia, MDS]) • Subclinical PNH (patients with a small population of PNH cells and no clinical or laboratory evidence of hemolysis or thrombosis)
	Patients with PNH have a median survival of ten years after diagnosis. The approach to therapy depends on the severity of symptoms and the degree of hemolysis. The treatment options for PNH are supportive care, allogenic hematopoietic stem cell transplantation (HCT) and a complement blockade.(2-3)
Efficacy	Empaveli (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.(1)
	The efficacy and safety of Empaveli in patients with PNH were assessed in a randomized, open-label, active comparator-controlled, 16-week Phase 3 study (Study APL2-302; NCT03500549). The study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with hemoglobin (Hb) levels less than 10.5 g/dL.(1)
	Eligible patients entered a 4-week run-in period during which they received Empaveli 1,080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomized in a 1:1 ratio to receive either 1,080 mg of Empaveli twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period. If required due to a lactate dehydrogenase (LDH) greater than 2 X the upper limit of normal (ULN), the dose of Empaveli could be adjusted to 1,080 mg every three days.(1)
	The efficacy of Empaveli was based on change from baseline to Week 16 (during randomized controlled period) in Hb 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 randomized controlled period, and change from baseline to Week 16 in absolute reticulocyte count (ARC).(1)

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Empaveli was superior to eculizumab for the change from baseline in Hb level at Week 16 (P<0.0001). The adjusted mean change from baseline in Hb level was 2.37 g/dL in the group treated with Empaveli versus -1.47 g/dL in the eculizumab group, demonstrating an adjusted mean increase of 3.84 g/dL with Empaveli compared to eculizumab at week 16 (95% CI, 2.33-5.34).(1)

Non-inferiority was demonstrated in the endpoints of transfusion avoidance and change from baseline in ARC.(1)

Study APL2-308 enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrollment and with Hb levels less than the lower limit of normal. Eligible patients were randomized in a 2:1 ration to receive Empaveli or supportive care (control arm) (excluding complement inhibitors [e.g., transfusions, corticosteroids, supplements such as iron, folate, and vitamin B12]) through the duration of the 26-week treatment period. The efficacy of Empaveli was based on the percentage of patients achieving Hb stabilization, defined as avoidance of a > 1 g/dL decrease in Hb levels from baseline in the absence of transfusion, and the change from baseline in LDH level. Supportive efficacy data included change from baseline in ARC, change from baseline in Hb, and transfusion avoidance, defined as the proportion of patients who did not require a transfusion through Week 26. Baseline was defined as the average of measurements recorded prior to taking the first dose of Empaveli or prior to randomization to the control arm treatment group. Efficacy results are shown below.(1)

	Empaveli	Control Arm	Difference (95% CI) p-value
Hb Stabilization (n, %)	30 (85.7%)	0 (0%)	73% (57%,89%) p<0.0001
Change from Baseline in LDH (Least Square [LS] Mean CFB, Standard Error [SE])	-1870 (101.0)	-400 (313.3)	-1470 (-2113.4,-827.3) p<0.0001
Change from baseline in ARC (LS, Mean CFB, SE)	-123 (9.2)	-19 (25.2)	-103 (-158.9, -48.7) p=0.0002)
Change from baseline in Hb (LS, Mean CFB, SE)	2.9 (0.38)	0.3 (0.76)	2.7 (0.99, 4.35) p=0.0019
Transfusion Avoidance (n, %)	32 (91%)	1 (6%)	72% (56%, 80%) p<0.0001

Safety	Empaveli contains the following boxed warnings:(1)

- 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 pneumoniae, Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B

  - Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria
  - Vaccinate patients against encapsulate bacteria as recommended at least 2 weeks prior to administering the first dose of Empaveli unless

<table>
<tr><td></td><td>risks of delaying Empaveli therapy outweigh the risks 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

• 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.(1)

Empaveli is contraindicated in:

• Patients with a 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</td></tr>
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REFERENCES

Number	Reference
1	Empaveli prescribing information. Apellis Pharmaceuticals, Inc. February 2024.
2	Sahin Fahri, Meltem Akay O, Ayer M, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016; 6(2): 19-27.
3	Rodolfo D. Cançado, Aderson da Silva Araújo, Alex Freire Sandes, Celso Arrais, Clarisse Lopes de Castro Lobo, Maria Stella Figueiredo, Sandra Fátima Menosi Gualandro, Sara Teresinha Olalla Saad, Fernando Ferreira Costa. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematology, Transfusion and Cell Therap. 2020.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Empaveli	pegcetacoplan subcutaneous soln	1080 MG/20ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Empaveli	Pegcetacoplan Subcutaneous Soln	1080 MG/20ML	8	Vials	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Empaveli	pegcetacoplan subcutaneous soln	1080 MG/20ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

	Initial Evaluation
	
	Target Agent(s) will be approved when ALL of the following are met:
	
	1. ONE of the following:
	   A. The patient has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as confirmed by flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (GPI) – linked proteins (lab tests required) **OR**
	   B. The patient has another FDA labeled indication for the requested agent **AND**
	2. If the patient has an FDA labeled indication, then ONE of the following:
	   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
	   B. There is support for using the requested agent for the patient's age for the requested indication **AND**
	3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
	4. The patient will NOT be using the requested agent in combination with Soliris (eculizumab) for the requested indication (NOTE: if the patient is switching from Soliris, Soliris should be continued for the first 4 weeks after starting the requested agent and then Soliris should be discontinued) **AND**
	5. The patient will NOT be using the requested agent in combination with Fabhalta (iptacopan) or Ultomiris (ravulizumab-cwvz) for the requested indication **AND**
	6. The patient does NOT have any FDA labeled contraindications to the requested agent
	
	Length of Approval: 12 months
	
	NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
	
	Renewal Evaluation
	
	Target Agent(s) will be approved when ALL of the following are met:
	
	1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**

Module	Clinical Criteria for Approval
	2. The patient has had improvements or stabilization with the requested agent (e.g., decreased requirement of RBC transfusions, stabilization/improvement of hemoglobin, reduction of lactate dehydrogenase (LDH), stabilization/improvement of symptoms) (medical records required) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with Fabhalta (iptacopan), Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met:
	
	1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**
	2. BOTH of the following:
	    A. The requested quantity (dose) exceeds the program quantity limit **AND**
	    B. ONE of the following:
	        1. The patient has a lactate dehydrogenase (LDH) level greater than 2X the upper limit of normal (lab test required) **OR**
	        2. ALL of the following: (medical records required)
	            A. The patient had a prior LDH greater than 2X the upper limit of normal and required a dose increase **AND**
	            B. The patient is currently using the requested dose **AND**
	            C. The requested quantity (dose) does NOT exceed 1,080 mg every three days
	
	Length of Approval: up to 12 months NOTE: If approving for every three days dosing approve a quantity of 10 vials/30 days for 12 months