09-J4000-04

Original Effective Date: 10/01/21

Reviewed: 02/11/26

Revised: 03/15/26

Subject: Pegcetacoplan (Empaveli)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

PNH is an uncommon, life-threatening hemolytic anemia; the incidence of PNH ranges from 0.1 to 0.2 per 100,000 persons per year. PNH results from an acquired genetic deficiency in the cytolytic complement cascade that renders red blood cells (RBCs) susceptible to lysis. Chronic destruction of PNH RBCs by complement leads to serious morbidities. Increased hemolysis at night, hypothesized to result from decreased blood pH and activation of the complement system, leads to characteristic bloody morning urination. Excessive or persistent intravascular hemolysis in persons with PNH results in anemia, hemoglobinuria, and complications related to the presence of plasma-free hemoglobin (e.g., thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension). Complement inhibitors are used in the treatment of PNH to reduce hemolysis and transfusion requirements.

Pegcetacoplan (Empaveli™) is an inhibitor of the complement protein C3 and the activation fragment C3b. Binding of C3 prevents intravascular hemolysis by regulating the downstream membrane attack complex while C3b inhibition prevents extravascular hemolysis. Pegcetacoplan is Food and Drug Administration (FDA) approved for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).It has also been FDA approved for the treatment of adults and pediatric patients 12 years and older with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN), to reduce proteinuria.

The efficacy and safety of pegcetacoplan for the treatment of PNH was compared to eculizumab in a randomized, open-label, 16-week study. Patients with PNH stabilized on eculizumab for at least 3 months with a hemoglobin of less than 10.5 g/dL were included. There was a 4-week period where patients received eculizumab and pegcetacoplan 1080 mg subcutaneously twice weekly before continuing pegcetacoplan as a single agent. There were 80 patients enrolled in the trial. The primary endpoint was the change from baseline to week 16 in hemoglobin level which was significantly improved with pegcetacoplan treatment as compared with eculizumab with an adjusted mean increase

of 3.84 g/dL (2.37 vs -1.47 g/dL; 95% CI, 2.33 to 5.34 g/dL). Secondary endpoints achieving noninferiority included transfusion avoidance (85% pegcetacoplan vs 15% eculizumab), change from baseline in mean absolute reticulocyte count (-136 vs 28 x 10^9cells/L). The change from baseline in LDH did not reach noninferiority (-15 vs -10 U/L), but there was a higher proportion of patients receiving pegcetacoplan who achieved normalization of LDH at the end of week 16 as compared to eculizumab (71% vs 15%). Numerical improvements on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale (ranges from 0-52, with a higher score indicating less fatigue) occurred in the group treated with pegcetacoplan (9.2 improvement from baseline). Two additional uncontrolled studies in patients with PNH not receiving a complement inhibitor have been conducted over a 1-year period also resulted in an increase in hemoglobin. Adverse reactions that occurred in patients treated with pegcetacoplan as compared with eculizumab included injection-site reactions(39% vs 5%), infections(29% vs 26%), diarrhea(22% vs 3%), abdominal pain (20% vs 10%), respiratory tract infection (15% vs 13%), viral infection (12% vs 8%), and fatigue(12% vs 23%), breakthrough hemolysis (10% vs 23%), headache (7% vs 23%), and chest pain (7% vs 3%).

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of pegcetacoplan (Empaveli) **meets the definition of medical necessity** when used to treat the following indications when the specific criteria are met:

1. **Paroxysmal Nocturnal Hemoglobinuria (PNH)**
    a. Flow cytometry to confirm PNH in both red and white blood cells (with at least 5% granulocyte or monocyte clone size) – documentation must be provided
    b. **ONE** of the following:
        i. Member's lactate dehydrogenase (LDH) is elevated (i.e., 1.5 times greater than the upper limit of normal [ULN] as determined by the laboratory performing the test) **and ONE** of the following:
            1. Member's disease is transfusion-dependent evidenced by 2 or more transfusions in the 12 months prior to pegcetacoplan initiation – documentation must be provided
            2. Member has a history of a major adverse vascular event (MAVE) from thromboembolism (e.g., myocardial infarction, cerebrovascular accident, deep vein thrombosis) – documentation must be provided
            3. Member has anemia with a hemoglobin less than the lower limit of normal – documentation must be provided.

ii. Member has been previously receiving eculizumab (Soliris, Bkemv, Epysqli), ravulizumab (Ultomiris), iptacopan (Fabhalta), or crovalimab (Piasky) for the treatment of PNH and is switching to pegcetacoplan (Empaveli)

c. **ONE** of the following:

i. Member has been vaccinated against encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis) at least 2 weeks prior to therapy initiation

ii. Member has been vaccinated against encapsulated bacteria less than 2 weeks prior to therapy initiation and will receive prophylactic antibiotics for at least 2 weeks following vaccination.

d. There is no evidence of an active infection caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B)

e. The member will not receive an additional complement inhibitor (e.g., crovalimab, danicopan, eculizumab and biosimilars, ravulizumab, or iptacopan)[a]

f. The dose does not exceed 1080 mg twice a week[b]

2. C3 glomerulopathy (C3G) or primary immune complex membranoproliferative glomerulonephritis (IC-MPGN)

a. Member's diagnosis of C3G or primary IC-MPGN is confirmed with kidney biopsy – biopsy report must be provided

b. Member's current (within 90 days) urine protein-to-creatinine ratio (UPCR) is greater than or equal to 1 g/g – laboratory documentation must be provided.

c. Member has an eGFR greater than or equal to 30 mL/min/1.73 m^2

d. **ONE** of the following – documentation must be submitted:

i. Member has been treated with a 3-month course of maximally tolerated angiotensin-converting enzyme inhibitor (ACE-inhibitor) or angiotensin receptor blocker (ARB) therapy and will continue treatment in combination with pegcetacoplan

ii. Member has been treated with a 3-month course of maximally tolerated sodium-glucose co-transporter-2 inhibitor (SGLT2) therapy and will continue treatment in combination with pegcetacoplan

iii. Member has an intolerance, hypersensitivity, or contraindication to **ALL** ACE-inhibitor,ARB or SGLT2 agents

e. Pegcetacoplan is prescribed by or in consultation with a nephrologist

f. Member will not receive therapy in combination with budesonide, sparsetan, or an additional complement inhibitor (crovalimab, danicopan, eculizumab and biosimilars, ravulizumab, or iptacopan)

g. **ONE** of the following:

i. Member has been vaccinated against encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis) at least 2 weeks prior to therapy initiation

ii. Member has been vaccinated against encapsulated bacteria less than 2 weeks prior to therapy initiation and will receive prophylactic antibiotics for at least 2 weeks following vaccination.

h. There is no evidence of an active infection caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B)

i. The dose does not exceed the following:

i. C3 glomerulopathy or primary IC-MPGN:

1. Adults: 1080 mg twice a week
2. Pediatric patients 12 years of age and older: does not exceed FDA label dosing (Table 1)

Approval duration: 6 months

Continuation of pegcetacoplan **meets the definition of medical necessity** when **ALL** of the following are met

1. The member has been previously approved for pegcetacoplan for the treatment of PNH, C3G,or primary IC-MPGN by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
2. Member has a history of beneficial response to pegcetacoplan therapy for the treatment of **ONE** of the following:
    a. Paroxysmal nocturnal hemoglobinuria (PNH) –examples of beneficial response include decreased requirement for transfusions, stabilization of hemoglobin, reduction of LDH – documentation must be provided
    b. C3 glomerulopathy or primary IC-MPGN - examples of beneficial response include decrease of UPCR ratio from baseline, decrease from baseline in proteinuria – lab documentation must be provided
3. Member has been revaccinated against encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis) at least 2 weeks prior to therapy initiation according to current medical guidelines for vaccination while on pegcetacoplan therapy
4. There is no evidence of an active infection caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B)
5. The member will not receive an additional complement inhibitor (e.g., crovalimab, eculizumab and biosimilars, ravulizumab, or iptacopan)
6. The dose does not exceed the following:
    a. PNH: 1080 mg twice a week[b]
    b. C3 glomerulopathy or primary IC-MPGN:
        i. Adults: 1080 mg twice a week
        ii. Pediatric patients 12 years of age and older: does not exceed FDA label dosing (Table 1)

Approval duration: 1 year

[a] When converting from eculizumab for the treatment of PNH, eculizumab should be continued for 4 weeks while initiating pegcetacoplan and then eculizumab should be discontinued. When switching from ravulizumab, initiate pegcetacoplan no more than 4 weeks after the last dose of ravulizumab.

[b] When used for PNH, the dose may be adjusted to 1080 mg every 3 days if the lactate dehydrogenase (LDH) level is greater than 2x the upper limit of normal (ULN) – documentation must be submitted.

Table 1: Dosing in pediatric patients age 12 to less than 18 years with C3G or primary IC-MPGN

Weight	First dose	Second dose	Maintenance
50 kg or higher	1080 mg	1080 mg	1080 mg twice weekly
35 kg to less than 50 kg	648 mg	810 mg	810 mg twice weekly
Less than 35 kg	540 mg	540 mg	648 mg twice weekly

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

PNH

- 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir of at least 20 mL or with an on-body injector.
- Dosage for patients switching from C5 inhibitors
    - To reduce the risk of hemolysis with abrupt treatment discontinuation:
    - For patients switching from eculizumab, initiate pegcetacoplan while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with pegcetacoplan
    - For patients switching from ravulizumab, initiate pegcetacoplan no more than 4 weeks after the last dose of ravulizumab.

C3G or Primary IC-MPGN

- Adults: 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir of at least 20 mL or with an on-body injector.
- Pediatric patients 12 years of age and older:

Table 1: Dosing in pediatric patients age 12 to less than 18 years with C3G or primary IC-MPGN

Weight	First dose	Second dose	Maintenance

50 kg or higher	1080 mg	1080 mg	1080 mg twice weekly
35 kg to less than 50 kg	648 mg	810 mg	810 mg twice weekly
Less than 35 kg	540 mg	540 mg	648 mg twice weekly

Dose Adjustments

- PNH: For lactate dehydrogenase (LDH) levels greater than 2 × the upper limit of normal (ULN), adjust the dosing regimen to 1,080 mg every three days. In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

Drug Availability

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

PRECAUTIONS:

Boxed Warning

- Meningococcal infections may occur in patients and may become rapidly life-threatening or fatal if not recognized and treated early. Use 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 encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose unless the risks of delaying 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.
- Prescribers must enroll in the Risk Evaluation and Mitigation Strategy (REMS).

Contraindications

- Patients with hypersensitivity to pegcetacoplan or any of the excipients.
- Patients with unresolved serious infection caused by encapsulated bacteria.

Precautions/Warnings

- 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).

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3490	Unclassified drugs

ICD-10 Diagnosis Codes That Support Medical Necessity

D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
N00.A	Acute nephritic syndrome with C3GN
N00.6	Acute nephritic syndrome with DDD
N00.B1	Acute nephritic syndrome with idiopathic IC-MPGN
N01.A	Rapidly progressive nephritic syndrome with C3GN
N01.6	Rapidly progressive nephritic syndrome with DDD
N02.A	Recurrent and persistent hematuria with C3GN
N02.6	Recurrent and persistent hematuria with DDD
N03.A	Chronic nephritic syndrome with C3GN
N03.6	Chronic nephritic syndrome with DDD
N04.A	Nephrotic syndrome with C3GN
N04.6	Nephrotic syndrome with DDD
N04.B1	Nephrotic syndrome with idiopathic IC-MPGN
N05.A	Unspecified nephritic syndrome with C3GN
N05.6	Unspecified nephritic syndrome with DDD
N06.A	Isolated proteinuria with C3GN
N06.6	Isolated proteinuria with DDD
N07.A	Hereditary nephropathy, not elsewhere classified with C3GN
N07.6	Hereditary nephropathy, not elsewhere classified with DDD

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if

based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

Paroxysmal nocturnal hemoglobinuria (PNH): A chronic acquired blood cell dysplasia with proliferation of a clone of stem cells producing erythrocytes, platelets, and granulocytes that are abnormally susceptible to lysis by complement; it is marked by episodes of intravascular hemolysis, causing hemolytic anemia, particularly following infections, and by venous thromboses, especially of the hepatic veins.

RELATED GUIDELINES:

Eculizumab (Soliris), 09-J1000-17

Iptacopan (Fabhalta), 09-J4000-80

Ravulizumab (Ultomiris), 09-J3000-26

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 2025 July 30]. Available from: http://www.clinicalpharmacology.com/.
2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025 July 30].
3. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021; 384: 1028-1037.
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [2025 May 1]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
5. Empaveli (pegcetacoplan)[package insert]. Apellis Pharmaceuticals, Inc. Waltham, MA. July 2025.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

10/01/21	New Medical Coverage Guideline.
10/15/21	Revision to guideline; consisting of updating the position statement.
07/15/22	Review and revision to guideline; consisting of updating the references.
09/15/23	Review and revision to guideline; consisting of updating the references.

05/15/24	Revision to update to vaccination requirement and agents not to be used in combination in the position statement. Update to contraindications and administration.
06/15/25	Review and revision to guideline; consisting of updating the agents not to be used in combination and updating references.
09/15/25	Review and revision to guideline; consisting of including C3 glomerulopathy and primary IC-MPGN into the position statement.
03/15/26	Review and revision to guideline; consisting of updating C3 glomerulopathy and primary IC-MPGN in the position statement.