Medical Drug Clinical Criteria

Subject:	Empaveli (pegcetacoplan)		
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Overview

This document addresses the use of Empaveli (pegcetacoplan), a subcutaneously administered peptide that targets complement C3. It is FDA approved for the treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH).

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare acquired hematopoietic stem cell disorder associated with a variety of nonspecific clinical features including but not limited to hemolytic anemia, fatigue, smooth muscle dystonia, and atypical venous thrombosis. Treatment options are limited but may include the use of therapeutic anticoagulation, allogeneic hematopoietic cell transplantation and/or complement inhibitors depending upon symptom severity, degree of hemolysis, and history of thrombosis. Eculizumab, ravulizumab, and crovalimab target complement C5 and are used to reduce intravascular hemolysis, decrease or eliminate the need for blood transfusions, and reduce the risk for thrombosis. Despite C5 inhibition, some patients continue to experience extravascular hemolysis, manifesting as persistent anemia, due to a separate complement C3 pathway. Empaveli is a subcutaneous treatment option and targets extravascular hemolysis through the C3 pathway. Current published evidence includes one phase 3, open-label, controlled trial that included individuals with hemoglobin levels lower than 10.5 g per deciliter and recent transfusion despite stable eculizumab therapy (Hillmen 2021). Compared to individuals continuing treatment with eculizumab, those treated with Empaveli achieved an adjusted mean hemoglobin increase of 3.84 g/dL at week 16. Another phase 3, open-label, controlled trial included individuals with PNH who were complement-inhibitor naïve with Lactate dehydrogenase (LDH) ≥1.5 times the upper limit of normal and hemoglobin level below the lower limit of normal (Wong 2023). Individuals treated with Empaveli achieved hemoglobin stabilization and a greater decrease in LDH level compared to individuals receiving supportive care.

Empaveli is available in 20 mL single use vials for subcutaneous use. It is administered by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir or via the Empaveli on-body injector. Individuals with a lactate dehydrogenase (LDH) level greater than 2x the upper limit of normal may adjust the dosing frequency to every 3 days. If complement inhibitor therapy is discontinued, individuals should be closely monitored for at least 8 weeks after cessation to detect hemolysis. The prescribing information includes instructions for individuals switching to Empaveli from C5 inhibitors. If switching from eculizumab, initiate Empaveli while continuing eculizumab at its current dose for 4 weeks. After 4 weeks, discontinue eculizumab and continue monotherapy with Empaveli. If switching from ravulizumab, initiate Empaveli no more than 4 weeks after the last dose of ravulizumab. No overlap therapy is recommended with ravulizumab.

Empaveli (pegcetacoplan) has a black box warning for serious infections caused by encapsulated bacteria. 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. Life-threatening and fatal infections with encapsulated bacteria have occurred in patients treated with complement inhibitors. Individuals should be immunized, according to most current Advisory Committee on Immunization Practices (ACIP) recommendations, against encapsulated bacteria at least 2 weeks prior to administering the first dose unless the risk of delaying therapy outweigh the risk of developing a serious infection. The FDA has required the manufacturer to develop comprehensive risk management programs that include the enrollment of prescribers in the Empaveli REMS Program. Additional information and forms for individuals, prescribers, and pharmacists may be found on the manufacturer's website: https://www.empaveli.com.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Empaveli (pegcetacoplan)

Initial requests for Empaveli (pegcetacoplan) may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as verified by flow cytometry, including the presence of (Parker 2005):
   A. PNH type III red cell clone or a measurable granulocyte or monocyte clone; **OR**
   B. Glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient polymorphonuclear cells (PMNs);

AND

III. Individual has completed or updated immunization against encapsulated bacteria, including *Streptococcus pneumoniae* and *Neisseria meningitidis* (serogroups A, C, W, and Y and serogroup B), at least 2 weeks prior to administration of the first dose of Empaveli (pegcetacoplan), unless the risks of delaying Empaveli outweigh the risk of developing a bacterial infection with an encapsulated organism;

AND

IV. One of the following applies (A or B):
   A. Individual is complement inhibitor treatment naïve (i.e. not switching from eculizumab or ravulizumab) (Wong 2023); **AND**
      1. Individual has lactate dehydrogenase greater than or equal to 1.5 times the upper limit of normal, and documentation is provided; **AND**
      2. Individual has one or more PNH-related sign or symptom (such as but not limited to anemia, history of a major adverse vascular event from thromboembolism, or history of transfusion due to PNH);

   OR

   B. Documentation is provided that individual is switching from treatment with eculizumab or ravulizumab (Hillmen 2021); **AND**
      1. If on eculizumab, treatment with eculizumab will be discontinued 4 weeks after Empaveli initiation, **OR**
      2. If on ravulizumab, treatment with ravulizumab will be discontinued prior to Empaveli initiation; **AND**
         a. Empaveli will be initiated no later than 4 weeks after the last dose of ravulizumab.

Initial Approval Duration: 6 months

Continuation requests for Empaveli (pegcetacoplan) may be approved if the following criteria are met:

I. Individual has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH); **AND**
II. Individual has completed or updated immunization against encapsulated bacteria, including *Streptococcus pneumoniae* and *Neisseria meningitidis (*serogroups A, C, W, and Y, and serogroup B); **AND**
III. Documentation is provided that individual has experienced a clinical response as shown by one of the following (Hillmen 2021):
   A. Stabilization of hemoglobin levels; **OR**
   B. Reduction in number of transfusions required; **OR**
   C. Improvement in hemolysis (for example, normalization or decrease of LDH levels).

Requests for Empaveli (pegcetacoplan) may not be approved for the following:

I. Individual is using in combination with iptacopan, danicopan, eculizumab, or ravulizumab [with the exception of a 4-week overlap for individuals switching from eculizumab to pegcetacoplan]; **OR**
II. If initiating therapy, individual has evidence of an active infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type B.

Quantity Limits

Empaveli (pegcetacoplan) Quantity Limits

Drug	Limit
Empaveli (pegcetacoplan) 1080 mg/20 mL (54 mg/mL) vial	10 vials per 30 days
Empaveli (pegcetacoplan) On-body injector	10 injectors per 30 days

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J3490 Unclassified drugs (when specified as [Empaveli])

C9399	Unclassified drugs or biologicals (When specified as [Empaveli])
ICD-10 Diagnosis	
	All diagnoses pend

Document History

Revised: 05/17/2024
Document History:

- 05/17/2024 – Select Review: Add danicopan to combination exclusion criteria; update vaccination requirements per label; update exclusion for active infection to apply to initiation of therapy. Coding Reviewed: No changes.
- 02/23/2024 – Select Review: Include meningococcal vaccination requirement in continuation of use criteria; update meningococcal vaccination to include all serogroups; specify Empaveli initiation timing after ravulizumab per label; include iptacopan combination in may not approve criteria. Coding Reviewed: No changes.
- 11/17/2023 – Annual Review: Update criteria to include age and expand use in treatment naïve individuals; update criteria for individuals switching treatment; move active infection statement to may not approve section; add quantity limit for Empaveli on-body injector. Coding Reviewed: No changes.
- 11/18/2022 – Annual Review: Move combination use exclusion to may not approve section. Coding Reviewed: No changes.
- 05/20/2022 – Select Review: No changes. Coding Reviewed: No changes.
- 11/19/2021 – Annual Review: Update quantity limit to 30-day limit. Coding reviewed: No changes.
- 05/21/2021 – Select Review: Add new criteria and quantity limit for Empaveli. Coding Reviewed: Added J3490, J3590, C9399. All diagnoses pend.

References

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