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 (Soliris or Ultomiris) depending upon symptom severity, degree of hemolysis, and history of thrombosis. Soliris and Ultomiris 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 the first subcutaneous treatment option and the first agent to target extravascular hemolysis. 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). FDA approval for PNH, including for complement inhibitor-naïve individuals, was based on data from the Phase 3 Hillmen study and 2 uncontrolled, unpublished studies in patients with PNH who were not receiving a complement inhibitor (NCT03593200; NCT02588833). These treatment-naïve studies included a total of 24 patients treated for approximately 1 year. The label notes that increases in hemoglobin were observed in these trials, but no additional data is provided. An additional phase 3 controlled trial is underway to study the effects on complement inhibitor-naïve individuals with PNH (NCT04085601), with results expected in 2021. Phase 3 data to support the safety and efficacy of Empaveli in treatment-naïve individuals has not been published to date.

Empaveli is available in 20 mL single use vials for subcutaneous use. It is administered by subcutaneous infusion twice weekly (i.e. day 1 and day 4 of each week) via a commercially available infusion pump with a reservoir. 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 Solirirs (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 Ultomiris (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. Meningococcal infections may occur in patients treated with Empaveli and may become rapidly life-threating 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. 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 has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as confirmed 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

II. Individual has been immunized against encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to administration of the first dose of Empaveli (pegcetacoplan), unless the clinical record documents the risks of delaying Empaveli outweigh the risk of developing a bacterial infection with an encapsulated organism;

AND

III. Individual has no evidence of an active infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B;

AND

IV. Individual is switching from treatment with eculizumab or ravulizumab; **AND**

V. Individual has persistent anemia despite C5 inhibitor treatment as defined by (Hillmen 2021):
   A. Hemoglobin <10.5 g/dL within the last 60 days, and documentation is provided; **AND**
   B. History of at least 1 transfusion in the last year, and documentation is provided;
      AND
   C. If on eculizumab, treatment with eculizumab will be discontinued 4 weeks after Empaveli initiation, **OR**
   D. If on ravulizumab, treatment with ravulizumab will be discontinued prior to Empaveli initiation.

Initial Approval Duration: 6 months

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

I. 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);
   AND

II. Individual is not using in combination with Soliris (eculizumab) or Ultomiris (ravulizumab).

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

I. Individual is using in combination with Soliris (eculizumab) or Ultomiris (ravulizumab) [with the exception of a 4-week overlap for individuals switching from eculizumab to pegcetacoplan].

Quantity Limits

Empaveli (pegcetacoplan) Quantity Limits

Drug	Limit
Empaveli (pegcetacoplan) 1080 mg/20 mL (54 mg/mL) vial	10 vials 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])
J3590	Unclassified biologics (when specified as [Empaveli])
C9399	Unclassified drugs or biologicals (when specified as [Empaveli])

ICD-10 Diagnosis

All diagnoses pend

Document History

Revised: 11/18/2022
Document History:

- 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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5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
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