Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Pegcetacoplan (Empaveli®)	MP-RX-FP-135-24	☒ MMM MA ☐ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of Pegcetacoplan (Empaveli®), a complement inhibitor approved by the Food and Drug Administration (FDA) for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Background Information

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). 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 (i.e. day 1 and day 4 of each week) 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 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),

Policy Name	Policy Number	Scope
Pegcetacoplan (Empaveli®)	MP-RX-FP-135-24	☒ MMM MA ☐ MMM Multihealth

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.

Approved Indications

Pegcetacoplan (Empaveli®) is indicated by the FDA for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Other Uses

None

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J3490	Unclassified drugs (when specified as [Empaveli])
C9399	Unclassified drugs or biologicals (When specified as [Empaveli])

ICD-10	Description
D59.5	Paroxysmal nocturnal hemoglobinuria

Policy Name	Policy Number	Scope
Pegcetacoplan (Empaveli®)	MP-RX-FP-135-24	☒ MMM MA ☐ MMM Multihealth

Medical Necessity Guidelines

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.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Pegcetacoplan (Empaveli®)

A. **Criteria For Initial Approval**

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 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 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.

Policy Name	Policy Number	Scope
Pegcetacoplan (Empaveli®)	MP-RX-FP-135-24	☒ MMM MA ☐ MMM Multihealth

B. **Criteria For Continuation of Therapy**

i. MMM considers continuation of Pegcetacoplan (Empaveli®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when the following criteria are met:

A. Documentation is provided that individual has experienced a clinical response as shown by one of the following (Hillmen 2021):

1. Stabilization of hemoglobin levels; **OR**
2. Reduction in number of transfusions required; **OR**
3. Improvement in hemolysis (for example, normalization or decrease of LDH levels);

AND

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

C. **Authorization Duration**

i. Initial Approval Duration: 6 months

ii. Reauthorization Approval Duration: 12 months

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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]; **OR**

ii. Individual has evidence of an active infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type B.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

Policy Name	Policy Number	Scope
Pegcetacoplan (Empaveli®)	MP-RX-FP-135-24	☒ MMM MA ☐ MMM Multihealth

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule
Pegcetacoplan (Empaveli®)	1,080 mg administered subcutaneously twice weekly (*Empaveli® is available as a 1080/20mL vial). Quantity limit: 10 vials per 30 days)
Exceptions	
Empaveli® dose should be adjusted in the following scenarios: • 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.	

Reference Information

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3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. *N Engl J Med*. 2021 Mar 18;384(11):1028-1037. PMID: 33730455. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2029073 Accessed on April 18, 2021. Supplementary Appendix available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2029073/suppl_file/nejmoa2029073_appendix.pdf. Accessed on October 9, 2021.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
6. Parker CJ, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005; 106(12):3699-3709.
7. Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv*. 2023;7(11):2468-2478.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption	N/A	6/28/2024

Revised: 01/29/2024