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),

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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.

Empaveli is available only through a restricted program called Empaveli REMS. 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

A. Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Other Uses

i. 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
J7799	NOC drugs, other than inhalation drugs, administered through DME [when specified as Empaveli (pegcetacoplan)]
C9399	Unclassified drugs or biologicals (When specified as [Empaveli])

ICD-10	Description

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D59.5	Paroxysmal nocturnal hemoglobinuria
N00.6	Acute nephritic syndrome with dense deposit disease
N00.A	Acute nephritic syndrome with C3 glomerulonephritis
N00.B1	Acute nephritic syndrome with idiopathic immune complex membranoproliferative glomerulonephritis (IC-MPGN)
N01.6	Rapidly progressive nephritic syndrome with dense deposit disease
N01.A	Rapidly progressive nephritic syndrome with C3 glomerulonephritis
N02.6	Recurrent and persistent hematuria with dense deposit disease
N02.A	Recurrent and persistent hematuria with C3 glomerulonephritis
N03.6	Chronic nephritic syndrome with dense deposit disease
N03.A	Chronic nephritic syndrome with C3 glomerulonephritis
N04.6	Nephrotic syndrome with dense deposit disease
N04.A	Nephrotic syndrome with C3 glomerulonephritis
N04.B1	Nephrotic syndrome with idiopathic immune complex membranoproliferative glomerulonephritis (IC-MPGN)
N05.6	Unspecified nephritic syndrome with dense deposit disease
N05.A	Unspecified nephritic syndrome with C3 glomerulonephritis
N06.6	Isolated proteinuria with dense deposit disease
N06.A	Isolated proteinuria with C3 glomerulonephritis
N07.6	Hereditary nephropathy, not elsewhere classified with dense deposit disease
N07.A	Hereditary nephropathy, not elsewhere classified with C3 glomerulonephritis

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.

Pegcetacoplan (Empaveli®)

A. Criteria For Initial Approval *(Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

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 meningitidiss (serogroups A, C, W, and Y and serogroup B),* 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; **AND**
    a. Empaveli will be initiated no later than 4 weeks after the last dose of ravulizumab.

OR

v. Individual is 12 years of age or older; **AND**

vi. Individual has a diagnosis of one of the following:

A. Complement 3 glomerulopathy (C3G); **OR**

B. Primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN); **AND**

vii. Documentation is provided that diagnosis has been verified with kidney biopsy; **AND**

viii. Diagnosis is NOT secondary to another condition (including but not limited to infection, malignancy, monoclonal gammopathy, a systemic autoimmune disease such as systemic lupus erythematosus, chronic antibody-mediated rejection, or a medication); **AND**

ix. Individual has had a trial of maximally tolerated angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy, unless contraindicated or not tolerated; **AND**

x. Individual has proteinuria ≥1 g/g; **AND**

xi. Individual has a urine protein-to-creatinine ratio (UPCR) ≥1 g/g; **AND**

xii. Individual has an eGFR ≥ 30 mL/min/1.73 m2; **AND**

xiii. Documentation is provided that individual will be taking Empaveli (pegcetacoplan) in combination with an angiotensinconverting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) unless contraindicated or not tolerated; **AND**

xiv. Individual has been immunized 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.

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. Individual has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH); **AND**
B. 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**
C. 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);

OR

D. Individual has a diagnosis of one of the following:
    1. Complement 3 glomerulopathy (C3G); **OR**
    2. Primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN); **AND**
E. Individual has been immunized against encapsulated bacteria, including Streptococcus pneumoniae and Neisseria meningitidis (serogroups A, C, W, and Y, and serogroup B); **AND**
F. Documentation is provided that individual will be taking Empaveli (pegcetacoplan) in combination with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) unless contraindicated or not tolerated; **AND**
G. There is clinically significant reduction in proteinuria.

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):

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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.

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

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	Limit
Empaveli® (pegcetacoplan) 1080 mg/20mL (54 mg/mL) vial	1,080 mg administered subcutaneously twice weekly using an infusion pump or Empaveli injector.	10 vials per 30 days
Empaveli® (pegcetacoplan) injector		10 injections 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. In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks. • Use of silica reagents in coagulation panels may result in artificially prolonged activated partial thromboplastin time (aPTT).

Reference Information

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1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: October 4, 2023.
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.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 11/20/2025	Add clinical criteria for new indications of Complement 3 Glomerulopathy (C3G) and Primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN); wording and formatting updates. Administrative update to add documentation. Coding Reviewed: Removed HCPCS NOC J3490 and added J7799. Removed all diagnosis pend. Added ICD-10-CM D59.5, N00.6, N00.A, N01.6, N01.A, N02.6, N02.A, N03.6, N03.A, N04.6, N04.A, N05.6, N05.A,	12/3/2025	12/11/2025

	N06.6, N06.A, N07.6, N07.A. Added ICD-10-CM N00.B1, N04.B1 effective 10/1/25.		
Annual Review 12/24/2024	Updated background information to add REMs program requirement for patients using Empaveli. Add danicopan to combination exclusion criteria; update vaccination requirements per label; update exclusion for active infection to apply to initiation of therapy. 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. Minor wording and formatting changes. Coding Reviewed: No changes.	3/20/2025	4/2/2025
Policy Inception 01/29/2024	Elevance Health's Medical Policy adoption	N/A	6/28/2024