pegcetacoplan (Empaveli™)

Policy # 00768
Original Effective Date: 12/13/2021
Current Effective Date: 06/12/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of pegcetacoplan (Empaveli™)‡ for the treatment of paroxysmal nocturnal hemoglobinuria to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for pegcetacoplan (Empaveli) will be considered when the following criteria are met for the requested drug:

I. Initial Therapy
   A. Patient has received vaccination against meningococcal infections within 2 years prior to, or at the time of initiating the requested drug; AND
   B. If the drug is initiated <2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics until 2 weeks after vaccination; AND
   C. Patient is 18 years of age or older; AND
   D. Documentation is provided of peripheral blood high sensitivity flow cytometry results showing a granulocyte or monocyte clone size of ≥5%; AND
   E. Patient meets ONE of the following (i OR ii):
      i. Patient has at least ONE of the following significant disease manifestations caused by hemolysis (a, b, c, d, OR e):
         a) Documented history of a major adverse vascular event (MAVE) from thromboembolism; OR
         b) Presence of organ damage secondary to chronic hemolysis (e.g., worsening renal insufficiency); OR

c) Patient is transfusion-dependent as evidenced by 2 or more transfusions in the 12 months prior to initiation of treatment; OR
d) Patient has a high lactate dehydrogenase (LDH) activity (defined as ≥1.5 x the upper limit of normal) with clinical symptoms (e.g., severe fatigue, dyspnea, jaundice, abdominal or chest pain, discolored urine, dysphagia, pulmonary hypertension); OR
e) Patient has symptomatic anemia with a hemoglobin less than the lower limit of normal; OR

ii. Patient has been previously receiving eculizumab (Soliris®)‡ or ravulizumab (Ultomiris™)‡ for the treatment of PNH and is switching to pegcetacoplan (Empaveli); AND
*(Note: These specific patient criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

F. For a patient transitioning to Empaveli from eculizumab (Soliris) or ravulizumab (Ultomiris), the prescriber attests that these medications will be discontinued within 4 weeks after starting Empaveli.

II. Continuation therapy
A. Patient has received an initial authorization for Empaveli; AND
B. Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
i. Decreased serum LDH compared to pretreatment baseline; OR
ii. Decreased need for blood transfusion compared to pretreatment baseline; OR
iii. Stabilization of hemoglobin; AND
*(Note: These specific patient criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
C. Empaveli will not be used in combination with Soliris or Ultomiris.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of pegcetacoplan (Empaveli) when the patient does not have a manifestation of significant disease or has not been previously

receiving eculizumab (Soliris) or ravulizumab (Ultomiris) for PNH to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of pegcetacoplan (Empaveli) when the patient has not demonstrated improvement in PNH disease manifestations while on therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of pegcetacoplan (Empaveli) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Background/Overview

Empaveli is a C3 complement inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in adults. It is the first treatment for PNH that binds to complement protein C3 and acts proximally in the complement cascade to control both C3b-mediated extravascular hemolysis and terminal complement-mediated intravascular hemolysis. It should be dosed as 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir of at least 20 mL. Other treatments available for PNH include the C5 complement inhibitors Soliris and Ultomiris. These products are each administered via an intravenous infusion. It should be noted that Empaveli was demonstrated to be superior to Soliris in clinical trials and also has the advantage of easier administration.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is an acquired hematopoietic stem cell disorder associated with an acquired somatic mutation of the phosphatidylinositol glycan class A (PIGA) gene. Mutations disrupt the first step in glycophosphatidylinositol (GPI) synthesis, which causes an absence of the GPI anchor and a deficiency of GPI proteins. The absence of GPI proteins on erythrocytes makes them susceptible to attack by complement and intravascular hemolysis. Intravascular hemolysis associated with PNH leads to release of free hemoglobin, leading to anemia, hemoglobinuria, thrombosis, dysphagia,

abdominal pain, pulmonary hypertension, renal impairment, and erectile dysfunction. The prevalence of PNH is estimated to be between 0.5-1.5 per million people in the general population, with an approximately equal male to female distribution. Although PNH can affect any age group, the median age at diagnosis is during the fourth decade of life. The primary clinical finding is hemolysis of red blood cells by complement, which leads to hemoglobinuria that is most prominent in the morning. Those with PNH are also susceptible to repeated, potentially life-threatening thromboses. Underlying bone marrow dysfunction may also be present and those who are severely affected may have pancytopenia. Many patients also have acquired aplastic anemia. Although less common, some patients have concomitant myelodysplasia. For unknown reasons, PNH may rarely develop into acute leukemia.

Signs and symptoms of PNH may vary, with some patients exhibiting mild and stable disease for many years while other patients have severe symptoms that rapidly progress to life-threatening. However, chronic hemolysis is central to all of the symptoms and physical findings associated with PNH. Fatigue, rapid heartbeat, headaches, and chest pain and difficulty breathing while exercising can result from mild hemolysis. With severe hemolysis, disabling fatigue, dysphagia, and painful contractions of the abdomen and esophagus may occur. It is estimated that 15-30% of patients with PNH develop blood clots, particularly venous thrombosis. Diagnosis of PNH is suspected in those with unexplained hemoglobinuria or abnormally high serum lactate dehydrogenase (LDH) levels. However, flow cytometry is the main diagnostic test for the identification of PNH cells.

There are no formal guidelines for treatment of PNH. However, there is an expert opinion for management of PNH published in a journal supported by the American Society of Hematology. Diagnosis of PNH is straightforward based on flow cytometry and specific treatment is recommended based on classification by the PNH interest group. Soliris is recommended for patients with classic PNH characterized by >50% of GPI-AP-deficient PMNs as well as patients with PNH in the setting of another bone marrow failure syndrome with large PNH clones. No specific PNH therapy is recommended for patients with subclinical PNH with no clinical or biochemical evidence of intravascular hemolysis. This review was published before the approval of Ultomiris or Empaveli.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Empaveli was approved in May 2021 for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy and safety of Empaveli in patients with PNH were assessed in a randomized, open-label, active comparator-controlled, 16-week, study. The study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels less than 10.5 g/dL.

Eligible patients entered a 4-week run-in period during which they received Empaveli 1,080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomized in a 1:1 ratio to receive either 1,080 mg of Empaveli twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period. If required, the dose of Empaveli could be adjusted to 1,080 mg every 3 days. Empaveli was administered as a subcutaneous infusion over 20 to 40 minutes. Following completion of the randomized controlled period, all patients entered a 32-week open-label period and received monotherapy with Empaveli. All patients who completed the 48-week period were eligible to enroll in a separate long-term extension study.

A total of 80 patients were randomized to receive treatment, 41 to Empaveli and 39 to eculizumab. The efficacy measure of Empaveli was based on change from baseline to Week 16 in hemoglobin level. Baseline was defined as the average of measurements recorded prior to the taking the first dose of Empaveli. At the end of Week 16, Empaveli was found to be superior to eculizumab in the change in hemoglobin level ($p<0.0001$). The adjusted mean change from baseline in hemoglobin level was 2.37 g/dL in the Empaveli group versus -1.47 g/dL in the eculizumab group, demonstrating

an adjusted mean increase of 3.84 g/dL with Empaveli compared to eculizumab at Week 16 (95% CI, 2.33-5.34).

An additional study (the PRINCE study) was conducted in patients with PNH who were treatment-naïve to complement inhibitors. Although this study has not been completed, interim results showed that a statistically significant majority of patients (86%) treated with Empaveli over 26 weeks achieved hemoglobin stabilization compared with 0% of patients treated with non-complement inhibitor standard of care ($p<0.0001$).

References

1. Empaveli [package insert]. Apellis Pharmaceuticals, Inc. Waltham, MA. Updated August 2021.
2. Empaveli Drug Evaluation. Express Scripts. Updated May 2021.
3. PRINCE Study Topline Results. Data on file. Apellis Pharmaceuticals, Inc. Waltham, MA.

Policy History

Original Effective Date: 12/13/2021
Current Effective Date: 06/12/2023

11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. New policy.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Updated initial criteria to allow for coverage in patients with symptomatic anemia or who have previously received Soliris or Ultomiris for the treatment of PNH.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2024

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.