pegcetacoplan (Empaveli™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO235

Description

Pegcetacoplan (Empaveli) is a subcutaneous complement inhibitor of C3.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pegcetacoplan (Empaveli)	1,080 mg/20 mL vial	Paroxysmal nocturnal hemoglobinuria (PNH)	160 mL (8 vials)/28 days

Initial Evaluation

I. Pegcetacoplan (Empaveli) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or immunologist; **AND**
   C. Provider attestation that therapy will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]) (Note: overlapping therapy to comply with switch therapy guidance is allowed, *see Appendix*); **AND**
   D. Provider attestation of a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed via flow cytometry; **AND**
   E. Member has at least one of the following indications for treatment (chart notes required):
      1. Transfusion dependence (hemoglobin is 7 g/dL or less)
      2. Hemoglobin is 9 g/dL or less with symptoms of anemia
      3. The member has experienced a thromboembolic event
      4. Presence of organ damage secondary to chronic hemolysis
      5. High LDH activity (≥ 1.5 x ULN) with clinical symptoms; **AND**
   F. Documentation of baseline value for ALL of the following (chart notes required, necessary for renewal):
      1. Hemoglobin
      2. LDH level
      3. Reticulocytes
      4. Number of transfusions over the last year

II. Pegcetacoplan (Empaveli) is considered investigational when used for all other conditions, including but not limited to:
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
   B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors
   C. Amyotrophic lateral sclerosis (ALS)
   D. Glomerulopathy or glomerulonephritis
   E. Macular degeneration
   F. Hemolytic uremic syndrome
   G. Myasthenia gravis
   H. Neuromyelitis optica spectrum disorder (NMOSD)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation that medication will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]); **AND**
IV. Member has exhibited improvement or stability of disease symptoms as evidenced by at least one of the following:
   - Increase in hemoglobin
   - Reduction in LDH
   - Reduction in reticulocyte count
   - Reduction in transfusion frequency

Supporting Evidence

I. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by complement-mediated hemolysis, leading to debilitating fatigue, anemia, dyspnea, bone pain, bleeding/bruising, thrombosis, and bone marrow dysfunction. Curative therapy for PNH is allogenic hematopoietic stem cell (HSC) transplant; however, given safety and cost limitations, transplant is reserved for those with severe and refractory disease manifestations.
II. Diagnosis and treatment of this condition is highly specialized. To ensure appropriate diagnosis and that benefits of treatment outweigh risks, prescribing by, or in consultation with, a specialist is required. Confirmation of diagnosis by Flow Cytometry is currently the most accepted method

to confirm diagnosis of PHN; this is required given the rarity of PNH and to ensure medication is medically necessary.

III. Treatment for PNH is indicated when signs and symptoms are present. This includes transfusion dependence, symptoms of anemia, thrombosis, organ dysfunction, and debilitating fatigue associated with hematologic lab values that are out of the normal range.

IV. The C5 inhibitors, eculizumab (Soliris) and ravulizumab (Ultomiris) (± supportive care), have become standard of care given their ability to improve disease manifestations. However, these only target intravascular hemolysis, leaving opportunity for extravascular hemolysis in the liver and spleen. Despite treatment, anemia and need for continued blood transfusions may persist in some patients. For the majority of patients C5 inhibitors are successful treatment options as they have shown to improve Hg, LDH levels, reticulocyte count, and/or reduce transfusion frequency. The safety profile of these therapies is well established.

V. Pegcetacoplan (Empaveli) is a C3 complement inhibitor, and acts proximally to the complement cascade, preventing intravascular and extravascular hemolysis. It is the first complement inhibitor that may be self-administered - via a subcutaneous infusion pump. However, therapy may also be administered by a healthcare provider. Therapy that is being administered by a healthcare professional should be billed through the member's medical benefit.

VI. To date, pegcetacoplan (Empaveli) has been evaluated in adult patients. Clinical trials are underway to evaluate the safety and efficacy in pediatric patients. Other therapies [e.g., ravulizumab (Ultomiris)] have been evaluated and are FDA-approved down to one month of age. Until sufficiently evaluated in pediatric patients, pegcetacoplan (Empaveli) should be reserved for the FDA-approved age group(s) given the availability of alternatives avenues of care (e.g., other FDA-approved medications, enrolment in clinical trials).

VII. The pivotal trial for this therapy was an open-label, randomized, Phase 3 study in comparison to eculizumab (Soliris) (PEGASUS trial). Patients were 18 years of age or older, had a hemoglobin of less than 10.5 mg/dL (mean 8.7 g/dL) while on stable doses of eculizumab (Soliris) for at least three months before enrollment, 75% received a blood transfusion in the last year (over 50% of patients received four or more).

VIII. Eighty patients were enrolled in the trial. Seventy-five percent had received a blood transfusion in the last year (over 50% of patients received four or more). Primary outcome: change in Hg from baseline at week 16. Secondary outcomes: proportion of transfusion-free patients, change in reticulocyte count, lactate dehydrogenase (LDH) level, and Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The normalization of hematologic variables was also evaluated. Endpoints were tested in a hierarchical manner, the primary outcome was tested for superiority, and the secondary outcomes were tested for non-inferiority (NI). The primary outcome met superiority, and transfusion rate and reticulocyte count met NI. Normalization of hematologic variables (Hg, reticulocytes, LDH) were favorable for pegcetacoplan (Empaveli). Pegcetacoplan (Empaveli) was also evaluated in Phase 1 and 2 open-label, single-arm trials in complement inhibitor-naïve patients. Improvements were seen in Hg, LDH, reticulocytes, and FACIT-F scores in a small number of patients.

IX. The safety and efficacy of pegcetacoplan (Empaveli) has been established for 1,080 mg (20 mL) twice weekly. In the clinical trials, three patients discontinued therapy given lack of efficacy.

Following, a protocol amendment was made to allow an increase in the dose to every three days, and two patients received the increased dose. Data regarding safety and efficacy of greater than 1,080 mg (20 mL) twice weekly has not been disclosed and real-world studies are underway to evaluate increasing the frequency to every three days.

X. With the exception of the four-week overlap to get patients established on pegcetacoplan (Empaveli), therapy has not been evaluated in combination with other complement inhibitors. It is advised that complement inhibitors are not abruptly discontinued. If switching from eculizumab (Soliris), therapy should be overlapped for four weeks with pegcetacoplan (Empaveli). For those switching from ravulizumab (Ultomiris), pegcetacoplan (Empaveli) should be started no more than four weeks after the last dose of ravulizumab (Ultomiris). Maintenance therapy with more than one complement inhibitor therapy is not expected to have additional efficacy, and is expected to have serious safety implications (e.g., serious infections caused by encapsulated bacteria). Thus, maintenance on more than one complement inhibitor therapy is not indicated at this time.

XI. The bulk of evidence is from patients that were refractory to C5 inhibitor, eculizumab (Soliris), and it is expected that pegcetacoplan (Empaveli) will be utilized heavily in this treatment setting; however, given the alternative protein target of this therapy, coupled with evidence data support from Phase 1 and 2 trials, it is expected pegcetacoplan (Empaveli) will be efficacious as a first-line treatment. A clinical trial is underway to evaluate this further.

Investigational or Not Medically Necessary Uses

I. Pegcetacoplan (Empaveli) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
   B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors
   C. Amyotrophic lateral sclerosis (ALS)
   D. Glomerulopathy or glomerulonephritis
   E. Macular degeneration
   F. Hemolytic uremic syndrome
   G. Myasthenia gravis
   H. Neuromyelitis optica spectrum disorder

Appendix

I. Complement inhibitor administration:

Therapy	Dose/Frequency	Duration of medication coverage (maintenance)	Route
pegcetacoplan (Empaveli)	1,080 mg (20 mL) twice weekly	3-4 days	SQ
eculizumab (Soliris)	600 mg weekly for four weeks, 900 mg on the fifth week, then 900 mg every two weeks thereafter	2 weeks	IV
ravulizumab (Ultomiris)	One loading dose (based on weight) 2,400 mg-3,000 mg, then maintenance treatment (based on weight) starting two weeks later: 3,000 mg – 3,600 mg every eight weeks	8 weeks	IV

II. Switch therapy guidance:

- Transitioning from eculizumab (Soliris) to pegcetacoplan (Empaveli): Overlap therapy for four weeks (i.e., initiate pegcetacoplan [Empaveli] while continuing eculizumab [Soliris] at the current dose). Then, discontinue eculizumab (Soliris) after four weeks of treatment with pegcetacoplan (Empaveli) - to utilize pegcetacoplan (Empaveli) as monotherapy.
- Transitioning from ravulizumab (Ultomiris) to pegcetacoplan (Empaveli): Once the last dose of ravulizumab (Ultomiris) is administered, pegcetacoplan (Empaveli) should be initiated within four weeks of the infusion. No further doses of ravulizumab (Ultomiris) should be administered while pegcetacoplan (Empaveli) treatment is active.
- Transitioning from eculizumab (Soliris) to ravulizumab (Ultomiris) or vice versa: reference prescribing information for guidance.

References

1. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021;384(11):1028-1037.
2. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology*. 2016(1):208-216.
3. Empaveli [Prescribing Information]. Apellis Pharmaceuticals, Inc. May 2021.
4. Apellis Pharmaceuticals, Inc. Phase Iia, Open Label, Multiple Dose Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneously Administered Apl-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (Pnh). clinicaltrials.gov; 2020.
5. Apellis Pharmaceuticals, Inc. A Phase Ib, Open Label, Multiple Ascending Dose, Pilot Study to Assess the Safety, Preliminary Efficacy and Pharmacokinetics of Subcutaneously Administered Apl-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria(Pnh). clinicaltrials.gov; 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2021