Paroxysmal Nocturnal Hemoglobinuria Agents
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO235

Description
Pegcetacoplan (Empaveli) is a subcutaneous complement inhibitor of C3. Iptacopan (Fabhalta) is an oral complement factor B inhibitor.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pegcetacoplan (Empaveli)	Paroxysmal nocturnal hemoglobinuria (PNH)	1,080 mg/20 mL vial	160 mL (8 vials)/28 days
iptacopan (Fabhalta)		200 mg capsules	60 capsules/30 days

Initial Evaluation

I. **Pegcetacoplan (Empaveli)** and **iptacopan (Fabhalta)** 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 from anti-C5 therapy is allowed, *see Appendix*); **AND**
   D. Provider attestation of a diagnosis of **paroxysmal nocturnal hemoglobinuria** (**PNH**) confirmed via flow cytometry with PNH clones of at least 10%; **AND**
   E. Member has at least one of the following indications for treatment:
      1. Transfusion dependence (hemoglobin is 7 g/dL or less)
      2. Hemoglobin is 9 g/dL or less with symptoms of anemia (e.g. disabling fatigue)
      3. The member has experienced a thromboembolic event
      4. Presence of organ damage secondary to chronic hemolysis (e.g., renal insufficiency, pulmonary insufficiency/hypertension)
      5. High LDH activity (≥ 1.5 x ULN) with clinical symptoms
      6. Patient has symptoms associated with smooth muscle dystonia (e.g., abdominal pain, dysphagia, esophageal spasm, erectile dysfunction); **AND**
   F. The request is for pegcetacoplan (Empaveli); **OR**
      1. The request is for iptacopan (Fabhalta); **AND**

i. Documentation that treatment with pegcetacoplan (Empaveli) has been ineffective, contraindicated, or not tolerated.

II. Pegcetacoplan (Empaveli) and iptacopan (Fabhalta) are 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)
   I. Thrombotic microangiopathy
   J. IgA nephropathy
   K. Immune thrombocytopenia
   L. Immunoglobulin A (IgA) vasculitis (Henoch-Schoenlein purpura) in pediatric patients
   M. Immunoglobulin A (IgA) nephropathy

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 (e.g., increased 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; therefore, this is required given the rarity of PNH and to ensure medication is medically necessary. Of note the proportion of PNH III cells, which are cells completely missing GPI-anchored proteins on the cell surface, can be diluted by a recent transfusion or depleted due to a recent hemolytic crisis.

III. Pegcetacoplan (Empaveli) and iptacopan (Fabhalta) have not been evaluated in combination with other complement inhibitors. There is currently one open-label, single-arm, phase 2 trial that is evaluating the use of iptacopan (Fabhalta) and eculizumab (Soliris) combination use; however, study results are not mature. Therefore, the efficacy and safety of combination use remains unknown at this time.

IV. Treatment for PNH is indicated when signs and symptoms are present with a diagnosis confirmed via flow cytometry. Signs and symptoms include transfusion dependence (defined as a Hgb ≤7 g/dL), symptoms of anemia with a Hgb ≤9 g/dL, thrombosis, organ dysfunction, and debilitating fatigue associated with hematologic lab values that are out of the normal range (e.g., low Hgb, increased LDH, etc.). Smooth muscle dystonia can occur due to hemolysis induced depletion of nitric oxide, and is associated with abdominal pain, dysphagia, erectile dysfunction, and esophageal spasm. Nitric oxide depletion or pulmonary emboli can also be associated with pulmonary hypertension in some patients. The chronic hemolysis and associated anemia experienced by PNH patients can lead to disabling fatigue along with acute and chronic kidney disease. Anemia, and therefore the need for transfusions, can be multifactorial with hemolysis, iron deficiency, and bone marrow failure all of which contribute to low Hgb levels. The increased risk of thrombosis in PNH has a variety of potential contributing factors to the hypercoagulability state including prothrombotic microparticles, high levels of free Hgb, complement activation, and the absence/deficiency of GPI-linked proteins.

V. 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 the 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.

VI. **Pegcetacoplan (Empaveli)**

- 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; although, 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.
- To date, pegcetacoplan (Empaveli) has been evaluated in adult patients. Clinical trials are underway to evaluate the safety and efficacy of 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 alternate avenues of care (e.g., other FDA-approved medications, enrolment in clinical trials).

- The pivotal trial for pegcetacoplan (Empaveli) 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).
- 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.
- 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 the safety and efficacy of 1,080 mg (20mL) three times a week has been proven in scientific literature, and the pegcetacoplan (Empaveli) prescribing information recommends adjusting the dosing to 1,080mg (20 mL) every three days for lactate dehydrogenase (LDH) levels greater than 2× the upper limit of normal (ULN).
- 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.

- 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.

VII. **Iptacopan (Fabhalta)**

- The safety and efficacy of iptacopan (Fabhalta) was evaluated in two Phase 3, multicenter, open-label trials. Both trials were studied in adult patients aged 18 years and older. Safety and efficacy has not been evaluated pediatric patients.
- The APPPLY-PNH trial was a 24-week multicenter, open-label, randomized, Phase 3 trial which compared iptacopan (Fabhalta) against standard of care (SOC), eculizumab (Soliris) or ravulizumab (Ultomiris), in adult patients with PNH, as evidenced by a diagnosis via high-sensitivity flow cytometry with a clone size ≥10% and a hemoglobin less than 10 g/dL. Patients were required to be on a stable dose of eculizumab (Soliris) or ravulizumab (Ultomiris) for at least 6 months prior to randomization and 56% of patients had received a blood transfusion in the 6 months prior to enrollment. The primary endpoint was the percentage of participants achieving a hematological response, defined as an increase from baseline in Hb ≥2 g/dL in the absence of RBC transfusions, and demonstrated statistically significant change compared to SOC (difference: 80.3% [95% CI: 71.3-87.6]; p<0.0001). The other primary endpoint, percentage of participants achieving sustained Hb ≥12 g/dL in the absence of RBC transfusions, also demonstrated statistical significance compared to SOC (difference: 67.0% [95% CI: 56.3-76.9]; p<0.0001).
- The APPOINT-PNH trial was an open-label, single arm, Phase 3 trial that enrolled 40 treatment naïve, adult patients with a high-sensitivity flow cytometry clone size of ≥10%, Hgb <10 g/dL, and a LDH >1.5 ULN. The primary endpoint, percentage achieving hematological response, defined as an increase from baseline in Hb ≥2 g/dL in the absence of RBC transfusions, was met (92.2% (95% CI: 82.5-100)). One key secondary endpoint was percentage achieving hematological response defined as having Hb ≥12 g/dL in the absence of RBC transfusions, which was also met (62.8% (95% CI: 47.5-77.5)).
- The safety and efficacy of iptacopan (Fabhalta) has been established for 200mg capsules twice daily. In the APPLY trial 82.3% of patients experienced a TEAE as compared to 80% of the comparator group. The most common TEAEs in the iptacopan (Fabhalta) group were headache (16.1%), diarrhea (14.5%), and nasopharyngitis (11.3%). Serious TEAEs occurred in 9.7% of the iptacopan (Fabhalta) patients while 14.3% of patients in the comparator group experienced a serious

TEAE. No patient in the iptacopan (Fabhalta) group experienced a hemolysis related serious TEAE while one patient in the comparator group experienced breakthrough hemolysis and another experienced extravascular hemolysis. No patients discontinued due to adverse events or deaths. In the APPOINT trial, no breakthrough hemolysis events or MAVEs were reported during the 24-week core treatment period. TEAEs were reported in 93% of patients with 65% considered mild in severity. The most common TEAEs were headache (27.5%), COVID-19 (15%), and upper respiratory tract infection (12.5%). Serious TEAEs were reported in 10% of patients with one case of bacterial pneumonia, COVID-19, type II diabetes mellitus, and cataract. No patients discontinued due to side effects and no deaths were reported.

- Both iptacopan (Fabhalta) and pegcetacoplan (Empaveli) have studies (APPLY-PNH and PEGASUS, respectively) demonstrating their efficacy in patients who were not clinically stable on anti-C5 therapy. There are no direct comparison trials available demonstrating superiority of iptacopan (Fabhalta) to pegcetacoplan (Empaveli), the use of the most cost-effective treatment option should be considered. For these reasons, trial of pegcetacoplan (Empaveli) is required prior to use of iptacopan (Fabhalta), unless contraindicated, not tolerated, or ineffective.

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
iptacopan (Fabhalta)	200 mg twice daily	1 day	PO
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 iptacopan (Fabhalta): initiate iptacopan (Fabhalta) no later than one week after the last dose of eculizumab (Soliris).
- Transitioning from ravulizumab (Ultomiris) to iptacopan (Fabhalta): initiate iptacopan (Fabahalta) no later than 6 weeks after the last dose of ravulizumab (Ultomiris).
- Transitioning from eculizumab (Soliris) to ravulizumab (Ultomiris) or vice versa: reference prescribing information for guidance.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added iptacopan (Fabhalta) capsules to the policy. Updated supporting evidence and other investigational conditions.	02/2024
Policy created	08/2021