Pharmacy Policy Bulletin: J-1099 Empaveli (pegcetacoplan) and Fabhalta (iptacopan) – Commercial and Healthcare Reform	
Number: J-1099	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1. and 2.):** **1.** Empaveli: Miscellaneous Specialty Drugs Injectable = Yes w/ Prior Authorization **2.** Fabhalta: Miscellaneous Specialty Drugs Oral = Yes w/Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-1099-007	**Original Date:** 08/04/2021
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Drugs Product(s):	• Empaveli (pegcetacoplan) • Fabhalta (iptacopan)

FDA-Approved Indication(s):	• Empaveli (pegcetacoplan)
	  ○ Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
	• Fabhalta (iptacopan)
	  ○ Treatment of adult patients with PNH
	  ○ Reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 gm/gm.
	  ○ Treatment of adults with complement 3 glomerulopathy (C3G), to reduce proteinuria.

Background:	• Empaveli is a subcutaneous infusion complement inhibitor for the treatment of adult patients with PNH. Empaveli can be administered via a commercially available pump or with the Empaveli Injector. Empaveli binds to complement proteins C3 and C3b and inhibits downstream activation of proteins in the complement pathways. Inhibition of complement pathways prevents both extravascular (EVH) and intravascular hemolysis (IVH). • Fabhalta (iptacopan) is a self-administered, oral complement factor B inhibitor indicated for the treatment of adults with PNH and reduction of proteinuria in adults with IgAN at risk of rapid disease progression. Fabhalta binds to Factor B of the alternative complement pathway and regulates the cleavage of C3, generation of downstream effectors, and the amplification of the terminal pathway. In PNH, IVH is mediated by the downstream membrane attack complex (MAC), EVH is facilitated by C3b opsonization. Fabhalta acts proximally in the alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement-mediated IVH. In IgAN, the deposition of

	galactose deficient IgA1 (Gd-IgA1) containing immune complexes in the kidney locally activates the alternative complement pathway which is thought to contribute to the pathogenesis of IgAN. By binding Factor B, iptacopan inhibits the effect of the alternative pathway. • PNH is a rare acquired hematopoietic stem cell disorder caused by a mutation of the phosphatidylinositol glycan class A (*PIGA*) gene in bone marrow stem cells. *PIGA*-mutant (PNH) cells lack all glycophosphatidyl inositol (GPI) anchored proteins, including CD55 and CD59, two essential complement regulatory proteins. The deficiency of CD55 and CD59 makes PNH red blood cells (RBCs) susceptible to complement-mediated hemolysis and a propensity for thrombosis. • The American Society of Hematology's 2016 Update on the Diagnosis and Management of Paroxysmal Nocturnal Hemoglobinuria states that PNH is diagnosed through flow cytometry analysis of blood cells, including red blood cells and polymorphonuclear cells. • The percentage of PNH clone and the percentage of GPI-AP-deficient polymorphonuclear cells vary between patients, and the American Society of Hematology did not propose a specific lower threshold for the diagnosis of PNH. • Presence of PNH clone (> 0%) or presence of GPI-AP-deficient polymorphonuclear cells (PMNs) (> 0%) based on flow cytometry and clinical symptoms can be used to diagnose PNH. • Patients with PNH may present with one or more of the following signs and symptoms: fatigue, lethargy, asthenia, abdominal pain, dyspnea, chest pain, odynophagia, erectile dysfunction in men, thrombosis, hemoglobinuria, anemia. Thrombosis in patients with PNH may lead to complications that shorten these patients' lifespan. • IgAN, also known as Berger's disease, is an autoimmune disorder where there are increased levels of a galactose-deficient immunoglobulin A (IgA) variant in the blood. Galactose-deficient IgA antibodies produced on mucosal B-cells in the ileum form immune complexes around the IgA. As the kidneys filter blood, these immune complexes damage the glomeruli and cause inflammation, kidney remodeling, and proteinuria. IgAN can lead to end-stage renal disease (ESRD) as the damage progresses; up to 40% of adults with IgAN will develop ESRD after 20 years. It is estimated that 60,000 people in the United States have IgAN. • The 2021 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Management of Glomerular Diseases recommend that all patients with IgAN and proteinuria > 0.5 g/day be treated with a maximally tolerated dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), in addition to blood pressure management and lifestyle modifications (e.g., smoking cessation, dietary sodium restriction, and regular exercise). The guidelines define high risk of progression in IgAN as proteinuria > 0.75 – 1 g/day despite ≥ 90 days of optimized supportive care. • The KDIGO guidelines state that IgAN can only be diagnosed with a kidney biopsy; there are no validated diagnostic serum or urine biomarkers for IgAN. In patients with IgAN, results of immunofluorescence or immunoperoxidase staining upon renal biopsy will demonstrate the presence of dominant or co-dominant deposition of IgA. • C3G is a progressive kidney disease that damages the glomeruli, potentially leading to kidney failure. • C3G is an ultra-rare disease with an estimated incidence of one to three cases per million. Approximately 50% of patients living with C3G progress to kidney failure within 10 years of diagnosis, requiring lifelong dialysis and/or kidney transplantation.

- C3G is characterized by inflammation and damage to the kidney glomeruli. The disease stems from abnormal activation of the complement system, specifically the alternative pathway, leading to the deposition of complement products within the glomeruli. This deposition increases glomerular permeability, causing leakage of proteins and other molecules into the urine. The resulting loss of protein and impaired filtration lead to a buildup of waste products and toxins in the blood, disrupting the kidneys' ability to regulate electrolytes and fluid balance, ultimately causing progressive kidney damage.
- The diagnosis of C3G should be suspected in any patient who presents with hematuria and/or proteinuria, particularly if accompanied by kidney function impairment, hypertension, and a low serum C3 level.
- The Kidney Disease Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases recommends the following:
    - Patients with idiopathic immune-complex glomerulonephritis (ICGN) and proteinuria < 3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, use supportive therapy with renin-angiotensin system (RAS) inhibition alone.
    - Patients with idiopathic ICGN, a nephrotic syndrome, and normal or near-normal serum creatinine, try a limited treatment course of glucocorticoids.
    - Patients with idiopathic ICGN, abnormal kidney function (but without crescentic involvements), active urine sediment, with or without nephrotic-range proteinuria, add glucocorticoids and immunosuppressive therapy to supportive care.
    - Patients presenting with a rapidly progressive crescentic idiopathic ICGN, treat with high-dose glucocorticoids and cyclophosphamide.
    - In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe disease should be treated initially with mycophenolate mofetil (MMF) plus glucocorticoids, and if this fails, eculizumab should be considered.
    - For most patients with idiopathic ICGN presenting with an eGFR < 30 ml/min per 1.73 m^2, treat with supportive care alone.
- Fabhalta is the first FDA-approved treatment for C3G.
- ICD-10 Code Information:
    - ICD-10: D59.5 PNH
    - ICD-10: N02.3 “Recurrent and persistent hematuria with diffuse mesangial proliferative glomerulonephritis” may apply to Fabhalta; however, the prescriber must confirm that the member has a specific diagnosis of primary IgAN at risk of rapid disease progression.
    - ICD-10: N00.A, N01.A, N02.A, N03.A, N04.A, N05.A, N06.A, N07.A, N00.6, N01.6, N02.6, N03.6, N04.6, N05.6, N06.6, N07.6 C3G.
- Prescribing Considerations:
    - Empaveli and Fabhalta should be prescribed by or in consultation with a hematologist for the treatment of PNH; Fabhalta should be prescriber by or in consultation with a nephrologist for the treatment of IgAN of C3G.
    - Empaveli and Fabhalta have black box warnings for serious infections caused by encapsulated bacteria. In addition, both products are subject to REMS programs that require vaccinations at least 2 weeks prior to the first dose according to the Advisory Committee on Immunization Practices (ACIP).
    - Empaveli is supplied in a single-dose vial containing 1,080 mg/20 mL.
    - The recommended dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump or with an Empaveli injector.

	○ Elevated lactate dehydrogenase (LDH) is a marker of hemolysis. For lactate dehydrogenase (LDH) levels greater than 2 times the upper limit of normal (ULN), the dosing regimen of Empaveli can be adjusted to 1,080 mg every three days. ○ Fabhalta is available as a 200 mg oral capsule. The recommended dosage of Fabhalta is 200 mg orally twice daily without regard to food. If a dose or doses are missed, advise the patient to take one dose of Fabhalta as soon as possible, even if it is soon before the next scheduled dose; then resume the regular dosing schedule. ○ In the treatment of PNH, Empaveli should not be used concomitantly with Soliris (eculizumab), Ultomiris (ravulizumab) or Fabhalta (iptacopan); Fabhalta should not be used concomitantly with Soliris, Ultomiris, or Empaveli. ○ Filspari (sparsentan) and Tarpeyo (budesonide) are two alternative medications indicated to slow/reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression that can be used instead of Fabhalta. Although Filspari, Tarpeyo, and Fabhalta all have different mechanisms of action, they all demonstrate similar effects on UPCR reduction.

Approval Criteria

I. Paroxysmal Nocturnal Hemoglobinuria (PNH) [Empaveli and Fabhalta]

A. Initial Authorization

When a benefit, coverage of Empaveli or Fabhalta for the treatment of PNH may be approved when all of the following criteria is met **(1. through 6.)**:

1. The member is 18 years of age or older.

2. The member has a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) (ICD-10: D59.5)

3. The member meets one (1) of the following **(a. or b):**
- **a.** The member has PNH mutant clones confirmed by flow cytometry.
- **b.** The member has glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient polymorphonuclear cells (PMNs) confirmed by flow cytometry.

4. The member's baseline hemoglobin level is < 10.5 g/dL.

5. The member meets one (1) of the following criteria **(a., b., or c.):**
- **a.** Elevated lactate dehydrogenase (LDH) ≥ 1.5 times the upper limit of normal (ULN).
- **b.** History of a thromboembolic event (e.g., deep vein thrombosis [DVT], pulmonary embolism [PE].
- **c.** Clinical findings of systemic complications (e.g., fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, erectile dysfunction, history of blood cell transfusion due to PNH).

6. The prescriber attests that Empaveli will not be used in combination with another complement inhibitor for PNH (e.g., Soliris, Ultomiris, Fabhalta), unless initially cross-titrating from Soliris or Ultomiris to Empaveli. Fabhalta will not be used in combination with another complement inhibitor for PNH (e.g., Soliris, Ultomiris, Empaveli), unless initially cross-titrating from

B. Reauthorization

When a benefit, reauthorization of Empaveli of Fabhalta may be approved when all of the following criteria are met **(1. and 2**.**)**:

1. The prescriber attests that the member has experienced a positive clinical response defined as one of the following **(a., b., or c.):**
   - **a.** Achieved hemoglobin stabilization or an increase from baseline.
   - **b.** Decrease from baseline in the number of transfusions.
   - **c.** Decrease from baseline in the LDH levels or reduction of hemolysis.
2. The prescriber attests that Empaveli will not be used in combination with another complement inhibitor for PNH (e.g., Soliris, Ultomiris).

C. Quantity Level Limits (Empaveli only)

When prior authorization is approved, coverage of additional quantities of Empaveli may be authorized in quantities as follows when the following criterion is met **(1.)**:

1. The member has LDH levels greater than 2 times the ULN per the laboratory reference range.
   - **a.** *Note: If approved, enter a patient level authorization (PLA) of 10 vials per 30 days.*
   - **b.** *Note: The coded quantity level limit is at 8 vials per 28 days.*

II. Primary Immunoglobulin A Nephropathy (IgAN) [Fabhalta]

A. Initial Authorization

When a benefit, coverage of Fabhalta for the treatment of IgAN may be approved when all of the following criteria are met **(1. through 5.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of IgAN, confirmed by biopsy (No ICD-10 code).
3. The member is at risk of for rapid disease progression, evidenced by one (1) of the following **(a. or b.)**:
   - **a.** Urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g
   - **b.** Proteinuria ≥ 1 g/day
4. The member has experienced therapeutic failure, contraindication, or intolerance to a maximally tolerated dose of one (1) of the following **(a. or b.)**:
   - **a.** Angiotensin converting enzyme (ACE) inhibitor
   - **b.** Angiotensin receptor blocker (ARB)
5. The member has experienced therapeutic failure, contraindication, or intolerance to both of the following plan-preferred products **(a. and b.):**
   - **a.** Filspari (sparsentan)
   - **b.** Tarpeyo (budesonide)

B. Reauthorization

When a benefit, reauthorization of Fabhalta may be approved when the following criterion is met **(1.)**:

1. The member has experienced a reduction in the UPCR or proteinuria from baseline.

III. Complement 3 Glomerulopathy (C3G) [Fabhalta]

A. Initial Authorization

When a benefit, coverage of Fabhalta for the treatment of C3G may be approved when all of the following criteria are met **(1. through 5.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of complement 3 glomerulopathy (C3G) (ICD-10: N00.A, N01.A, N02.A, N03.A, N04.A, N05.A, N06.A, N07.A, N00.6, N01.6, N02.6, N03.6, N04.6, N05.6, N06.6, N07.6 C3G) confirmed by biopsy.
3. The member is experiencing all of the following **(a. and b.):**
   - **a.** Urine protein-to-creatinine ratio (UPCR) ≥ 1.0 g/g
   - **b.** Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2.

4. The member has experienced therapeutic failure, contraindication, intolerance, or inadequate response to at least one (1) of the following **(a., b. or c.):**
   - **a.** Systemic corticosteroids
   - **b.** Immunosuppressants
   - **c.** Mycophenolate mofetil
5. The member is currently receiving the maximally tolerated dose or has experienced intolerance or contraindication to one (1) of the following **(a. or b.)**:
   - **a.** Angiotensin converting enzyme (ACE) inhibitor
   - **b.** Angiotensin receptor blocker (ARB)

B. Reauthorization

When a benefit, reauthorization of Fabhalta may be approved when the following criterion is met **(1.):**

1. The member has experienced a reduction in the UPCR from baseline.

IV. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

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14. Filspari [package insert]. San Diego, CA: Travere Therapeutics, Inc.; September 2024.
15. Tarpeyo [package insert]. Stockholm, Sweden: Calliditas Therapeutics AB; June 2024.
16. UpToDate, C3 Glomerulopathies: Dense Deposit Disease and C3 Glomerulonephritis. Available at: https://www.uptodate.com. Accessed March 28, 2025.
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Pharmacy policies do not constitute medical advice, nor are they intended to govern physicians' prescribing or the practice of medicine. They are intended to reflect the plan's coverage and reimbursement guidelines. Coverage may vary for individual members, based on the terms of the benefit contract.

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