09-J4000-80

Original Effective Date: 04/01/24

Reviewed: 02/14/24

Revised: 05/15/24

Subject: Iptacopan (Fabhalta®) Capsules

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Paroxysmal Nocturnal Hemoglobinuria (PNH) is an uncommon, life-threatening hemolytic anemia; the incidence of PNH ranges from 0.1 to 0.2 per 100,000 persons per year. PNH results from an acquired genetic deficiency in the cytolytic complement cascade that renders red blood cells (RBCs) susceptible to lysis. Chronic destruction of PNH RBCs by complement leads to serious morbidities. Increased hemolysis at night, hypothesized to result from decreased blood pH and activation of the complement system, leads to characteristic bloody morning urination. Excessive or persistent intravascular hemolysis in persons with PNH results in anemia, hemoglobinuria, and complications related to the presence of plasma-free hemoglobin (e.g., thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension). Extravascular hemolysis in PNH can also occur and result in reticuloendothelial destruction in the liver and spleen. Complement inhibitors are used in the treatment of PNH to reduce hemolysis and transfusion requirements.

Iptacopan (Fabhalta) is an inhibitor of factor B of the alternative complement pathway and regulates the cleavage of C3, the downstream effectors, and amplification of the terminal pathway. This prevents terminal complement-mediated intravascular hemolysis and controls C3b-mediated extravascular hemolysis. Iptacopan is Food and Drug Administration (FDA) approved for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

The approval of iptacopan was based on an open-label 24-week trial in patients with PNH with residual anemia (hemoglobin less than 10 g/dL) despite prior complement C5 inhibitors (eculizumab or ravulizumab use for at least 6 months prior to randomization) and from an open-label single-arm trial in treatment-naïve patients with PNH. The first trial in treatment experienced patients met its co-primary endpoint at 24 weeks with a higher proportion of patients treated with iptacopan achieving a hemoglobin (Hb) increase of ≥2 g/dL from baseline without the need for blood transfusions (82.3% vs 0%, $p<0.0001$), and a higher proportion of patients achieved sustained Hb levels of ≥12 g/dL without the

need for transfusions compared to patients who received complement C5 inhibitors (67.7% vs 0%, p<0.0001). All secondary endpoints also favored the use of iptacopan over the subjects who continued to receive alternative complement C5 inhibitors: percentage of patients avoiding transfusion (95.2% vs 45.7%, p<0.0001), adjusted mean hemoglobin change from baseline (3.6 vs -0.1, p<0.0001), and absolute reticulocyte count change from baseline (-116 vs 0, p<0.0001). The second trial in treatment naïve patients met the primary endpoint of the proportion of patients treated with iptacopan achieving ≥2 g/dL increases in Hb levels from baseline without the need for blood transfusions at 24 weeks [77.5% (95% CI, 61.5%, 89%)]. The most common adverse reactions included headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea and rash. Iptacopan has a Risk Evaluation and Mitigation Strategy (REMS) program due to the risk for serious and life-threatening infection caused by encapsulated bacteria, including Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of iptacopan (Fabhalta) **meets the definition of medical necessity** when:

1. **Paroxysmal Nocturnal Hemoglobinuria (PNH)**
    a. Flow cytometry to confirm PNH in both red and white blood cells (with at least 5% granulocyte or monocyte clone size) – documentation must be provided
    b. **ONE** of the following:
        i. Member's lactate dehydrogenase (LDH) is elevated (i.e., 1.5 times greater than the upper limit of normal [ULN] as determined by the laboratory performing the test) and **ONE** of the following:
            1. Member's disease is transfusion-dependent evidenced by 2 or more transfusions in the 12 months prior to iptacopan initiation – documentation must be provided
            2. Member has a history of a major adverse vascular event (MAVE) from thromboembolism (e.g., myocardial infarction, cerebrovascular accident, deep vein thrombosis) – documentation must be provided
            3. Member has anemia with a hemoglobin less than the lower limit of normal – lab documentation must be provided
        ii. Member has been previously receiving eculizumab (Soliris), pegcetacoplan (Empaveli), or ravulizumab (Ultomiris) for the treatment of PNH and has anemia with a hemoglobin less than the lower limit of normal – documentation must be provided

c. Member had an inadequate response or contraindication to at least **ONE** of the following – documentation must be provided[a]
    i. pegcetacoplan (Empaveli)
    ii. ravulizumab (Ultomiris)
d. The member will not receive an additional complement inhibitor (eculizumab, ravulizumab or pegcetacoplan) [b]
e. **ONE** of the following:
    i. Member has been vaccinated against encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis) at least 2 weeks prior to therapy initiation
    ii. Member has been vaccinated against encapsulated bacteria less than 2 weeks prior to therapy initiation and will receive prophylactic antibiotics for at least 2 weeks following vaccination.
f. There is no evidence of an active infection caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B)
g. The dose does not exceed 200 mg twice daily

Approval duration: 6 months

Continuation of iptacopan **meets the definition of medical necessity** when **ALL** of the following are met

1. Member has a history of beneficial response to iptacopan therapy for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) - examples of beneficial response include decreased requirement for transfusions, stabilization of hemoglobin, reduction of LDH – lab documentation must be provided
2. The member has been previously approved for iptacopan in the treatment of PNH by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
3. Member has been revaccinated against encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis) at least 2 weeks prior to therapy initiation according to current medical guidelines for vaccination while on iptacopan therapy
4. There is no evidence of an active infection caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B)
5. The member will not receive an additional complement inhibitor (eculizumab, ravulizumab or pegcetacoplan)[b]
6. The dose does not exceed 200 mg twice daily

Approval duration: 1 year

[a] Step not required if the member was previously treated with eculizumab.

[b] When converting from eculizumab, initiate iptacopan no later than 1 week after the last dose of eculizumab. When switching from ravulizumab, initiate iptacopan no later than 6 weeks after the last dose of ravulizumab.

NOTE: Quest Diagnostics® can perform the Flow cytometry assay (PNH with FLAER) used in the diagnosis of PNH.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Iptacopan is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria and is dosed 200 mg twice daily with or without food. Use is not recommended in patients with severe hepatic impairment or severe renal impairment.

PRECAUTIONS:

Boxed Warning

Iptacopan increases the risk of serious, life-threatening, or fatal infections caused by encapsulated bacteria and may become rapidly life-threatening or fatal if not recognized and treated early.

1. Immunize members against encapsulated bacteria at least 2 weeks prior to administering the first dose of iptacopan. See prescribing information if the patient is not up to date with vaccines against encapsulated bacteria.
2. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for encapsulated bacteria in persons receiving a complement inhibitor.
3. Monitor members for early signs of serious infections, and evaluate immediately if infection is suspected.
4. Enrollment in FABHALTA REMS is required for prescribers and pharmacies.

Contraindications

- Serious hypersensitivity to iptacopan or any of the excipients.
- Unresolved serious infection caused by encapsulated bacteria, including Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B.

Precautions/Warnings

- See boxed warning
- Monitor for PNH manifestations after discontinuation
- Monitor serum lipid parameters periodically during treatment and initiate cholesterol-lowering medication if indicated

Drug availability

- 200 mg capsules

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Paroxysmal nocturnal hemoglobinuria (PNH): A chronic acquired blood cell dysplasia with proliferation of a clone of stem cells producing erythrocytes, platelets, and granulocytes that are abnormally susceptible to lysis by complement; it is marked by episodes of intravascular hemolysis, causing hemolytic anemia, particularly following infections, and by venous thromboses, especially of the hepatic veins.

RELATED GUIDELINES:

Eculizumab (Soliris), 09-J1000-17

Pegcetacoplan (Empaveli), 09-J4000-04

Ravulizumab (Ultomiris), 09-J3000-26

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2024 [cited 2024 Jan 31]. Available from: http://www.clinicalpharmacology.com/.

2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2024 Jan 31].
3. Fabhalta (iptacopan) [package insert]. Novartis Pharmaceuticals Corp. East Hanover, NJ. March 2024
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [2024 Jan 31]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/14/24.

GUIDELINE UPDATE INFORMATION:

04/01/24	New Medical Coverage Guideline.
05/15/24	Revision to guideline including updating the vaccination requirement in the position statement.