09-J4000-80

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Reviewed: 04/09/25

Revised: 05/15/25

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). It has also been FDA approved to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to creatinine ration (UPCR) greater than or equal to 1.5 g/g. Continued approval of the IgAN indication is contingent upon verification of clinical benefit in a confirmatory clinical trial. Iptacopan is also FDA approved to reduce proteinuria in adults with complement 3 glomerulopathy.

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), ravulizumab (Ultomiris), or crovalimab (Piasky) 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 **BOTH** of the following – documentation must be provided

i. pegcetacoplan (Empaveli)

ii. ravulizumab (Ultomiris)

d. The member will not receive an additional complement inhibitor (crovalimab, danicopan, eculizumab, ravulizumab or pegcetacoplan)[a]

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

2. IgA nephropathy (IgAN)

a. Member's diagnosis of IgA nephropathy is confirmed with kidney biopsy – biopsy report must be provided

b. Member's current (within 90 days) urine protein-to-creatinine ratio (UPCR) is greater than or equal to 1.5 g/g – laboratory documentation must be provided.

c. Member has an eGFR greater than or equal to 30 mL/min/1.73 m^2

d. **ONE** of the following – documentation must be submitted:

i. Member has an inadequate response after a 3-month course of maximally tolerated ACE-inhibitor or ARB therapy

ii. Member has an intolerance to ACE-inhibitor or ARB therapy

iii. Member has a contraindication to **ALL** ACE-inhibitor or ARB agents

e. **ONE** of the following – documentation must be submitted:

i. Member has an inadequate response after a 6-month course of glucocorticoid therapy (e.g., methylprednisolone, prednisolone, prednisone)

ii. Member has an intolerance to glucocorticoid therapy

iii. Member has a contraindication to ALL glucocorticoid therapy

iv. Member has a comorbid condition and therapy with glucocorticoid therapy is not appropriate for the member

f. The member will continue on standard of care IgAN therapy (e.g., ACEI, ARB, SGLT2, aliskiren)

g. The member had an inadequate response or contraindication to BOTH of the following – documentation must be provided

   i. budesonide (Tarpeyo)

   ii. sparsetan (Filspari)

h. Iptacopan is prescribed by a nephrologist

i. Member will not receive therapy in combination with budesonide, sparsetan, or an additional complement inhibitor (crovalimab, danicopan, eculizumab, ravulizumab, or pegcetacoplan)

j. **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.

k. There is no evidence of an active infection caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B)

l. Dose does not exceed 200 mg twice daily

3. C3 glomerulopathy (C3G)

a. Member's diagnosis of C3G is confirmed with kidney biopsy – biopsy report must be provided

b. Member's current (within 90 days) urine protein-to-creatinine ratio (UPCR) is greater than or equal to 1 g/g – laboratory documentation must be provided.

c. Member has an eGFR greater than or equal to 30 mL/min/1.73 m^2

d. **ONE** of the following – documentation must be submitted:

   i. Member has an inadequate response after a 3-month course of maximally tolerated ACE-inhibitor or ARB therapy

   ii. Member has an intolerance to ACE-inhibitor or ARB therapy

   iii. Member has a contraindication to **ALL** ACE-inhibitor or ARB agents

e. **ONE** of the following – documentation must be submitted:

   i. Member has an inadequate response after a 6-month course of glucocorticoid therapy (e.g., methylprednisolone, prednisolone, prednisone)

   ii. Member has an intolerance to glucocorticoid therapy

   iii. Member has a contraindication to **ALL** glucocorticoid therapy

   iv. Member has a comorbid condition and therapy with glucocorticoid therapy is not appropriate for the member

f. The member has an inadequate response after a 3-month course or a contraindication to mycophenolate mofetil or mycophenolate sodium – documentation must be provided

g. The member will continue on standard of care C3G therapy (e.g., ACEI, ARB, mycophenolate mofetil/sodium, SGLT2)

h. Iptacopan is prescribed by a nephrologist

i. Member will not receive therapy in combination with budesonide, sparsetan, or an additional complement inhibitor (crovalimab, danicopan, eculizumab, ravulizumab, or pegcetacoplan)

j. **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.

k. There is no evidence of an active infection caused by encapsulated bacteria (e.g., Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type B)

l. 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 **ONE** of the following:

   a. 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

   b. IgA nephropathy - examples of beneficial response include decrease of UPCR ratio from baseline, decrease from baseline in proteinuria – lab documentation must be provided

   c. C3 glomerulopathy - examples of beneficial response include decrease of UPCR ratio from baseline, decrease from baseline in proteinuria – lab documentation must be provided

2. The member has been previously approved for iptacopan in the treatment of PNH, IgAN, or C3G 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 therapy in combination with budesonide, sparsetan, or an additional complement inhibitor (eculizumab, ravulizumab or pegcetacoplan)

6. The dose does not exceed 200 mg twice daily

Approval duration: 1 year

[a] 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. It is also indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to creatinine ration (UPCR) greater than or equal to 1.5 g/g. Continued approval of the IgAN indication is contingent upon verification of clinical benefit in a confirmatory clinical trial. Iptacopan is indicated for the treatment of adults with complement 3 glomerulopathy, to reduce proteinuria.

Iptacopan is dosed orally 200 mg twice daily with or without food and capsules should be swallowed whole. Use is not recommended in patients with severe hepatic 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]
N02.B1	Recurrent and persistent immunoglobulin A nephropathy with glomerular lesion
N02.B2	Recurrent and persistent immunoglobulin A nephropathy with focal and segmental glomerular lesion
N02.B3	Recurrent and persistent immunoglobulin A nephropathy with diffuse membranoproliferative glomerulonephritis
N02.B4	Recurrent and persistent immunoglobulin A nephropathy with diffuse membranous glomerulonephritis
N02.B5	Recurrent and persistent immunoglobulin A nephropathy with diffuse mesangial proliferative glomerulonephritis
N02.B6	Recurrent and persistent immunoglobulin A nephropathy with diffuse mesangiocapillary glomerulonephritis
N02.A	Recurrent and persistent hematuria with C3GN
N03.A	Chronic nephritic syndrome with C3GN
N04.A	Nephrotic syndrome with C3GN
N05.A	Unspecified nephritic syndrome with C3GN
N06.A	Isolated proteinuria with C3GN
N07.A	Hereditary nephropathy, not elsewhere classified with C3GN

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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

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:

Budesonide (Tarpyo), 09-J4000-14

Crovalimab (Piasky), 09-J4000-95

Danicopan (Voydeya), 09-J4000-88

Eculizumab (Soliris), 09-J1000-17

Pegcetacoplan (Empaveli), 09-J4000-04

Ravulizumab (Ultomiris), 09-J3000-26

Sparsetan (Filspari), 09-J4000-48

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 2025 Mar 28]. Available from: http://www.clinicalpharmacology.com/.
2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025 Mar 28].
3. Fabhalta (iptacopan) [package insert]. Novartis Pharmaceuticals Corp. East Hanover, NJ. March 2025.
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [2025 Mar 25]. 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 04/09/25.

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.
12/15/24	Review and revision to guideline; updated position statement to include primary immunoglobulin A nephropathy (IgAN) revising criteria for paroxysmal nocturnal hemoglobinuria.
05/15/25	Review and revision to guideline; updated position statement to include complement 3 glomerulopathy (C3G).