Fabhalta (iptacopan) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
07-01-2024	07-01-2024

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Fabhalta® (iptacopan) Capsule	Treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH)		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Paroxysmal Nocturnal Hemoglobinuria	Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening, rare, multi-systemic disease developing as a result of somatic mutation of hematopoietic stem cells, and characterized by clonal, complement-mediated intravascular hemolysis. PNH is mainly a disease of adults with a median age of onset in the thirties. High Precision Flow Cytometry is the most useful and accepted diagnostic test to confirm the diagnosis of PNH. Flow cytometry is performed by incubating the patient's peripheral blood cells with fluorescently-labeled monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI) anchored proteins, which are reduced or absent on blood cells in PNH. Since different blood cell lineages display different combinations of GPI-linked proteins, and some proteins bind to cell surfaces via both GPI-linked and GPI-independent mechanisms, it is recommended that at least two independent flow cytometry reagents be used on at least two cell lineages (e.g., RBCs and WBCs) to establish the diagnosis of PNH.(2) Lack of the complement inhibitor CD59 on the red blood cells surface is mostly responsible for the clinical manifestations in PNH. These patients manifest with chronic intravascular hemolysis, paroxysmal flares of hemolysis and a propensity for thrombosis. Intravascular hemolysis leads to release of free hemoglobin (Hb) into the blood. Free hemoglobin, in turn, can cause various toxic effects, including hypercoagulability, changes in vascular tone from reduction of circulating nitric oxide and renal damage.(3) Extravascular hemolysis also occurs in patients with PNH because C3 fragments that are not destroyed by the membrane attack complex (MAC) intravascularly can accumulate on the GPI-negative red blood cell (lacking CD55) surface and these fragments opsonize the red blood cells, causing reticuloendothelial destruction in the liver and spleen.(3)

	The main clinical situations or diseases that should be considered in the differential diagnosis of PNH are:(3) • Coombs-negative hemolytic anemia (e.g., hemoglobinopathies, hereditary spherocytosis), microangiopathic hemolytic anemias, drug- or toxin-induced hemolysis/anemias, disseminated intravascular coagulation, and autoimmune hemolysis • Venous thrombosis in atypical sites, including myeloproliferative disorders; solid tumors associated with hypercoagulability; extrinsic compression of vessels, and; inherited/acquired thrombophilias • Anemia and/or other cytopenias related to bone marrow failure syndrome (e.g., aplastic anemia, MDS) PNH is classified into three different categories:(3) • Classic PNH (PNH with clinical and laboratory findings of intravascular hemolysis without any evidence of bone marrow deficiency) • PNH in the setting of another specified bone marrow disorder (evidence of hemolysis, as well as another specified bone marrow disorder [e.g., aplastic anemia, MDS]) • Subclinical PNH (patients with a small population of PNH cells and no clinical or laboratory evidence of hemolysis or thrombosis) Patients with PNH have a median survival of ten years after diagnosis. The approach to therapy depends on the severity of symptoms and the degree of hemolysis. The treatment options for PNH are supportive care, allogenic hematopoietic stem cell transplantation (HCT) and a complement blockade.(2,3)
Efficacy	Iptacopan 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, intravascular hemolysis is mediated by the downstream membrane attack complex, while extravascular hemolysis is facilitated by C3b opsonization. Iptacopan acts proximally in the alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement mediated IVH.(1) The efficacy of Fabhalta in adults with PNH was evaluated in a multi-center, open-label, 24-week active comparator-controlled trial (APPLY-PNH; NCT04558918). The study enrolled adults with PNH and residual anemia (hemoglobin < 10 g/dL) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization. Efficacy primary endpoints were established based on demonstration of superiority of switching to Fabhalta compared to continuing on anti-C5 therapy in achieving hematological response after 24 weeks of treatment, without a need for transfusion, by assessing the proportion of patients demonstrating:(1) • Sustained increase of greater than or equal to 2 g/dL in hemoglobin levels from baseline (hemoglobin improvement) • Sustained hemoglobin levels greater than or equal to 12 g/dL Secondary endpoints included:(1) • Transfusion avoidance • Change from baseline in hemoglobin levels • Change from baseline in absolute reticulocyte counts Patients with sustained increase of hemoglobin levels greater than or equal to 2 g/dL in the Fabhalta arm had an 82.3% response rate (95% CI) and the response rate in the Anti-C5 arm was 0%. Patients with sustained hemoglobin level greater than or

	equal to 12 g/dL in the absence of tranfusions in the Fabhalta arm had a 67.7% response rate (95% CI) and the response rate in the Anti-C5 arm was 0%.(1) Fabhalta was studied in a single arm study in adults with PNH who were not previously treated with a complement inhibitor (APPOINT-PNH; NCT04820530). Adult patients with PNH (RBC clone size greater than or equal to 10%), hemoglobin less than 10 g/dL, and LDH greater than 1.5 times the upper limit of normal received Fabhalta during the 24-week open-label core treatment period. In total, 77.5% (95% CI: 61.5%, 89.2%) of patients achieved a sustained increase (between Day 126 and Day 168) in hemoglobin levels from baseline of greater than or equal to 2 g/dL in the absence of RBC transfusions.(1)
Safety	Fabhalta has a boxed warning about the increased risk of serious and life-threatening infections, caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type B:(1) • Complete or update vaccination for encapsulated bacteria at least 2 weeks prior to the first dose of Fabhalta, unless the risks of delaying Fabhalta outweigh the risk of developing a serious infection. • Patients receiving Fabhalta are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Fabhalta is contraindicated in:(1) • Serious hypersensitivity to iptacopan or any of the excipients • Initiation in patients with unresolved serious infection caused by encapsulated bacteria Fabhalta is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called FABHALTA REMS.(1)

REFERENCES

Number	Reference
1	Fabhalta prescribing information. Novartis Pharmaceuticals Corporation. December 2023.
2	Sahin Fahri, Meltem Akay O, Ayer M, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016; 6(2): 19-27.
3	Rodolfo D. Cançado, Aderson da Silva Araújo, Alex Freire Sandes, Celso Arrais, Clarisse Lopes de Castro Lobo, Maria Stella Figueiredo, Sandra Fátima Menosi Gualandro, Sara Teresinha Olalla Saad, Fernando Ferreira Costa. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematology, Transfusion and Cell Therap. 2020.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Fabhalta	iptacopan hcl cap	200 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Fabhalta	iptacopan 200 mg capsules	200 MG	60	Capsules	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Fabhalta	iptacopan hcl cap	200 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Fabhalta	iptacopan 200 mg capsules	200 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) AND ALL of the following: 1. The diagnosis was confirmed by flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (GPI) – linked proteins (lab tests required) **AND** 2. The patient's hemoglobin is less than 10 g/dL (lab tests required) **AND** 3. If the patient has NOT been previously treated with complement inhibitor therapy (e.g., Empaveli [pegcetacoplan], Soliris [eculizumab], or Ultomiris [ravulizumab-cwvz]) BOTH of the following (lab tests required): A. The patient has red blood cell clone size greater than or equal to 10% **AND** B. The patient has a lactate dehydrogenase (LDH) level greater than 1.5 times the upper limit of normal (ULN) **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to Empaveli (pegcetacoplan), Soliris (eculizumab), or Ultomiris (ravulizumab-cwvz) **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to Empaveli (pegcetacoplan), Soliris (eculizumab), or Ultomiris (ravulizumab-cwvz) **OR** C. The patient has an FDA labeled contraindication to Empaveli (pegcetacoplan), Soliris (eculizumab), AND Ultomiris (ravulizumab-cwvz) **OR** D. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** E. The prescriber has provided documentation that Empaveli (pegcetacoplan), Soliris (eculizumab), AND Ultomiris (ravulizumab-cwvz) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **OR** B. The patient has another FDA labeled indication for the requested agent **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with Empaveli (pegcetacoplan), Soliris (eculizumab), or Ultomiris (ravulizumab-cwvz) for the requested indication **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent (e.g., decreased requirement of RBC transfusions, stabilization/improvement of hemoglobin, reduction of lactate dehydrogenase (LDH), stabilization/improvement of symptoms) (medical records required) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with Empaveli (pegcetacoplan), Soliris (eculizumab), or Ultomiris (ravulizumab-cwvz) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval**: Initial approval up to 6 months Renewal approval up to 12 months