iptacopan (Fabhalta®)

Policy # 00876
Original Effective Date: 06/10/2024
Current Effective Date: 06/10/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider iptacopan (Fabhalta®)‡ for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for iptacopan (Fabhalta) will be considered when the following criteria are met:

I. Initial
   A. Patient has received vaccination against meningococcal infections within 2 years prior to, or at the time of initiating the requested drug; AND
   B. If the drug is initiated < 2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics until 2 weeks after vaccination; AND
   C. Patient is 18 years of age or older; AND
   D. Documentation is provided of peripheral blood high sensitivity flow cytometry results showing a granulocyte or monocyte clone size of ≥ 5%; AND
   E. Patient meets ONE of the following (i or ii):
      i. Patient has at least ONE of the following significant disease manifestations caused by hemolysis (a, b, c, d, OR e):
         a. Documented history of a major adverse vascular event (MAVE) from thromboembolism; OR
         b. Presence of organ damage secondary to chronic hemolysis (e.g., worsening renal insufficiency); OR
         c. Patient is transfusion-dependent as evidenced by 2 or more transfusions in the 12 months prior to the initiation of treatment; OR

d. Patient has a high lactate dehydrogenase (LDH) activity (defined as ≥ 1.5 times the upper limit of normal) with clinical symptoms (e.g., severe fatigue, dyspnea, jaundice, abdominal or chest pain, discolored urine, dysphagia, pulmonary hypertension); OR
e. Patient has symptomatic anemia with a hemoglobin less than the lower limit of normal; OR

ii. Patient has been previously receiving eculizumab (Soliris®)‡ or ravulizumab (Ultomiris™)‡ or pegcetacoplan (Empaveli™)‡ for the treatment of PNH and is switching to iptacopan (Fabhalta); AND

*(Note: These specific patient selection criteria are additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

F. For a patient transitioning to iptacopan (Fabhalta) from eculizumab (Soliris), ravulizumab (Ultomiris), or pegcetacoplan (Empaveli); the prescriber attests that these medications will be discontinued within 4 weeks after starting Fabhalta.

II. Continuation

A. Patient has received an initial authorization for Fabhalta; AND
B. Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
   i. Decreased serum LDH compared to pretreatment baseline; OR
   ii. Decreased need for blood transfusion compared to pretreatment baseline; OR
   iii. Stabilization of hemoglobin; AND

   *(Note: These specific patient selection criteria are additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
C. Fabhalta will not be used in combination with Empaveli, Soliris, or Ultomiris.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of iptacopan (Fabhalta) when the patient does not have a manifestation of significant disease or has not been previously receiving eculizumab (Soliris), ravulizumab (Ultomiris), or pegcetacoplan (Empaveli) for PNH to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of iptacopan (Fabhalta) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Background/Overview

Fabhalta is a Factor B inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in adults. It works by binding to Factor B to regulate the cleavage of C3 and ultimately downregulate the complement activation that is responsible for many of the manifestations of PNH. It is an oral treatment dosed as 200 mg twice daily without regard to food. Because it is a complement inhibitor, Fabhalta carries a similar requirement to other complement inhibitors for vaccination against encapsulated bacteria prior to treatment as well as a black box warning regarding the risk for serious infections.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is an acquired hematopoietic stem cell disorder associated with an acquired somatic mutation of the phosphatidylinositol glycan class A (PIGA) gene. Mutations disrupt the first step in glycophosphatidylinositol (GPI) synthesis, which causes an absence of the GPI anchor and a deficiency of GPI proteins. The absence of GPI proteins on erythrocytes makes them susceptible to attack by complement and intravascular hemolysis. Intravascular hemolysis associated with PNH leads to release of free hemoglobin, leading to anemia, hemoglobinuria, thrombosis, dysphagia, abdominal pain, pulmonary hypertension, renal impairment, and erectile dysfunction. The prevalence of PNH is estimated to be between 0.5-1.5 per million people in the general population, with an approximately equal male to female distribution. Although PNH can affect any age group, the median age at diagnosis is during the fourth decade of life. The primary clinical finding is hemolysis of red blood cells by complement, which leads to hemoglobinuria that is most prominent in the morning. Those with PNH are also susceptible to repeated, potentially life-threatening thromboses. Underlying bone marrow dysfunction may also be present and those who are severely affected may have pancytopenia. Many patients also have acquired aplastic anemia. Although less

common, some patients have concomitant myelodysplasia. For unknown reasons, PNH may rarely develop into acute leukemia.

Signs and symptoms of PNH may vary, with some patients exhibiting mild and stable disease for many years while other patients have severe symptoms that rapidly progress to life-threatening. However, chronic hemolysis is central to all of the symptoms and physical findings associated with PNH. Fatigue, rapid heartbeat, headaches, and chest pain and difficulty breathing while exercising can result from mild hemolysis. With severe hemolysis, disabling fatigue, dysphagia, and painful contractions of the abdomen and esophagus may occur. It is estimated that 15-30% of patients with PNH develop blood clots, particularly venous thrombosis. Diagnosis of PNH is suspected in those with unexplained hemoglobinuria or abnormally high serum lactate dehydrogenase (LDH) levels. However, flow cytometry is the main diagnostic test for the identification of PNH cells.

There are no formal guidelines for treatment of PNH. However, there is an expert opinion for management of PNH published in a journal supported by the American Society of Hematology. Diagnosis of PNH is straightforward based on flow cytometry and specific treatment is recommended based on classification by the PNH interest group. Soliris is recommended for patients with classic PNH characterized by >50% of GPI-AP-deficient PMNs as well as patients with PNH in the setting of another bone marrow failure syndrome with large PNH clones. No specific PNH therapy is recommended for patients with subclinical PNH with no clinical or biochemical evidence of intravascular hemolysis. This review was published before the approval of Ultomiris, Empaveli, or Fabhalta.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Fabhalta was approved in December 2023 for the treatment of adults with paroxysmal nocturnal hemoglobinuria.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Fabhalta administered orally in adults with PNH was evaluated in a multi-center, open-label, 24-week, active comparator-controlled trial called APPLY-PNH. The trial enrolled 97 adults with PNH and residual anemia (hemoglobin < 10 g/dL) despite previous treatment with a stable regimen of an anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization. Patients were randomized in an 8:5 ratio to switch to Fabhalta 200 mg orally twice daily (n=62) or to continue anti-C5 treatment throughout the duration of the 24-week randomized controlled period. Randomization was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months. Following completion of the 24-week randomized controlled period, all patients were eligible to enroll in a 24-week treatment extension period and receive Fabhalta monotherapy. Subsequently, patients were eligible to enter a separate long-term extension study.

Efficacy was 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 both a sustained increase of $\geq$ 2 g/dL in hemoglobin levels from baseline and sustained hemoglobin levels of $\geq$ 12 g/dL. Fabhalta was statistically superior to anti-C5 therapy for both endpoints with 82.3% of the Fabhalta group achieving a sustained increase of hemoglobin levels $\geq$ 2 g/dL compared to 0 in the anti-C5 therapy group ($p<0.0001$). Similarly, 67.7% of patients in the Fabhalta group had a sustained hemoglobin level $\geq$12 g/dL compared to 0 of the patients in the anti-C5 therapy arm.

The efficacy of Fabhalta in patients with PNH who were not previously treated with a complement inhibitor was studied in the APPOINT-PNH trial, a single arm study that enrolled a total of 40 adults with PNH. All 40 patients received Fabhalta 200 mg orally twice daily during the 24-week open-label core treatment period. Subsequently, patients were eligible to enroll in a 24-week treatment extension period and continue to receive Fabhalta, followed by a separate long-term extension study.

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In total, 77.5% (95% CI: 61.5%, 89.2%) of patients achieved a sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions, based on central laboratory hemoglobin values. In a sensitivity analysis, 87.5% (95% CI: 73.2%, 95.8%) of patients achieved a sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions.

References

1. Fabhalta [package insert]. Novartis Pharmaceuticals, Corp. East Hanover, NJ. Updated March 2024.

Policy History

Original Effective Date: 06/10/2024
Current Effective Date: 06/10/2024
05/02/2024 Medical Policy Committee review
05/08/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 05/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.