Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Fabhalta®
Common Name: iptacopan
PDL Category: Complement Inhibitors

Comparable Products	Preferred Drug List Status
Soliris	Medical
Ultomiris	Medical

Pharmacology/Usage: Iptacopan, the active ingredient of Fabhalta®, is complement Factor B inhibitor. 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 paroxysmal nocturnal hemoglobinuria, intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC), while extravascular hemolysis (EVH) 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.

Indication: For the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

There is no pregnancy category for this medication; however, the risk summary indicates that available data from clinical trials with use in pregnant women are not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH in pregnancy. The use of Fabhalta® in pregnant women or women planning to become pregnant may be considered following an assessment of the risks and benefits. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 200mg.

Recommended Dosage: Vaccinate patients against encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis (serogroups A, C, W, Y, and B)*, and *Haemophilus influenzae* type B, per current Advisory Committee on Immunization Practices (ACIP) recommendations at least 2 weeks prior to initiation of Fabhalta®. If urgent Fabhalta® therapy is indicated in a patient who is not up to date with vaccines for *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B per ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. Healthcare providers who prescribe Fabhalta® must enroll in the Fabhalta® REMS.

The recommended dose is 200mg PO BID without regard to food. Swallow capsules whole; do not open, break or chew capsules. 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) and then to resume the regular dosing schedule.

To reduce the potential risk of hemolysis with abrupt discontinuation of other PNH therapies:

- For patients switching from eculizumab, start Fabhalta® no later than 1 week after the last dose of eculizumab.
- For patients switching from ravulizumab, start Fabhalta® no later than 6 weeks after the last dose of ravulizumab.

There is no available information regarding the timeframe for initiation of Fabhalta® after other PNH therapies.

Dose adjustment is not required with mild or moderate hepatic impairment. The use of Fabhalta® is not recommended in patients with severe hepatic impairment. Dose adjustments are not required with mild or moderate renal impairment. The use of Fabhalta® is not recommended in patients with severe renal impairment with or without hemodialysis.

Drug Interactions: Concomitant use of CYP2C8 inducers (e.g., rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of Fabhalta®. Monitor the clinical response and discontinue use of the CYP2C8 inducer if loss of efficacy of Fabhalta® is evident.

Concomitant use of strong CYP2C8 inhibitors (e.g., gemfibrozil) may increase iptacopan exposure, which may result in an increased risk for adverse reactions with Fabhalta®. Coadministration with a strong CYP2C8 inhibitor is not recommended.

Box Warning: Fabhalta® has a box warning regarding serious infections caused by encapsulated bacteria. Fabhalta®, a complement inhibitor, increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B. Life-threatening and fatal infections with encapsulated bacteria have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- Complete or update vaccination for encapsulated bacteria at least 2 weeks prior to the first dose of Fabhalta® unless the risks of delaying therapy with Fabhalta® outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor.
- Patients receiving Fabhalta® are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and assess immediately if infection is suspected.

Because of the risk of serious infections caused by encapsulated bacteria, Fabhalta® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Fabhalta® REMS.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Fabhalta®) minus reported % incidence for anti-C5 (eculizumab or ravulizumab) in Study APPLY-PNH. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included headache (16%), nasopharyngitis (0%), diarrhea (9%), abdominal pain (12%), bacterial infection (0%), nausea (7%), viral infection (0%), arthralgia (5%), thrombocytopenia (6%), dizziness (6%), systemic hypertension (6%), lipid disorder (6%), and rash (3%).

As discussed in the Box warning section, Fabhalta® increases a patient's susceptibility to serious, life-threatening or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* type B. The initiation of Fabhalta® treatment is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria. Because of the risk of serious infections caused by encapsulated bacteria, Fabhalta® is available only through a restricted program under a REMS called Fabhalta® REMS. Notable requirements of the Fabhalta® REMS include the following:

- Prescribers must enroll in the REMS, counsel patients about the risk of serious infections caused by encapsulated bacteria, and provide patients with the REMS educational materials.
- Providers must assess patient vaccination status for vaccines against encapsulated bacteria and vaccinate if needed per ACIP recommendations two weeks prior to the first dose of Fabhalta®.
- Prescribers must provide a prescription for antibacterial drug prophylaxis if treatment must be started urgently, and the patient is not up to date with vaccines against encapsulated bacteria per ACIP recommendations at least 2 weeks prior to the first dose of Fabhalta®.
- Pharmacies that dispense Fabhalta® must be certified in the Fabhalta® REMS and must verify prescribers are certified.

- Patients must receive counseling from the prescriber about the need to receive vaccinations against encapsulated bacteria per ACIP recommendations, the need to take antibiotics as directed by the prescriber, and the early signs and symptoms of serious infection.
- Patients must be instructed to carry the Patient Safety Card with them at all times during treatment and for 2 weeks following the last dose of Fabhalta®.
- Further information is available by calling 1-833-99FABHA or by visiting www.FABHALTA-REMS.com.

After discontinuing treatment with Fabhalta®, monitor patients closely for at least 2 weeks after the last dose for signs and symptoms of hemolysis. If discontinuation of Fabhalta® is necessary, consider alternative therapy. If hemolysis occurs after discontinuation of Fabhalta®, consider restarting treatment with Fabhalta®, if appropriate, or starting another treatment for PNH.

Fabhalta® increases total cholesterol, LDL-cholesterol, and serum triglycerides. Some patients required cholesterol-lowering medications. Monitor serum lipid parameters periodically during treatment with Fabhalta® and start cholesterol-lowering medication, if needed.

Contraindications:

- In patients with serious hypersensitivity to iptacopan or any of the excipients of the product.
- For initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type B.

Manufacturer: Novartis Pharmaceuticals Corporation

Analysis: The efficacy of Fabhalta® in adults with PNH was assessed in a multicenter, open-label, 24-week, active comparator-controlled trial (APPLY-PNH) that included adults with PNH and residual anemia (hemoglobin <10g/dl) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization. There were 97 patients who were randomized in an 8:5 ratio to switch to Fabhalta® 200mg PO BID (N=62) or to continue on anti-C5 treatment (US-approved and non-US-approved eculizumab product [N=23] or US-approved and non-US-approved ravulizumab product [N=12]) 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.

Patients were required to be vaccinated against *Neisseria meningitidis* and recommended to be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenza* type B. If the patient had not been previously vaccinated or if a booster was required, vaccination was administered at least 2 weeks prior to the first dose of study medication. If Fabhalta® was initiated earlier than 2 weeks after vaccination, antibacterial drug prophylaxis was administered.

Demographics and baseline characteristics were generally balanced between treatment groups, which are presented in the table below (adapted from the prescribing information). In addition, the mean time on prior anti-C5 treatment was 3.8 and 4.2 years for the Fabhalta® and anti-C5 groups, respectively. The baseline mean PNH RBC clone size (Type II + III) was 64.6% for Fabhalta® and 57.4% for the anti-C5 group.

	Statistics	Fabhalta® (N=62)	Anti-C5[1] (N=35)
Age (years)	Mean	51.7	49.8
Sex- female	n (%)	43 (69.4%)	24 (68.6%)
Race- white	n (%)	48 (77.4%)	26 (74.3%)

	Statistics	Fabhalta® (N=62)	Anti-C5[1] (N=35)
Ethnicity- not Hispanic or Latino	n (%)	51 (82.3%)	27 (77.1%)
Hemoglobin level (g/dL)	Mean	8.9	8.9
LDH level (U/L) (lactate dehydrogenase-LDH)	Mean	269	273
Absolute reticulocyte count (10^9/L)	Mean	193	191
At least 1 transfusion in 6 mths prior to randomization	n (%)	35 (56.5%)	21 (60%)
Disease duration (years)	Mean	11.9	13.5

[1] eculizumab or ravulizumab

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: a sustained increase of ≥2g/dL in hemoglobin levels from baseline (hemoglobin improvement); and sustained hemoglobin levels ≥12g/dL. Other endpoints included transfusion avoidance, change from baseline in hemoglobin levels, and change from baseline in absolute reticulocyte counts (ARCs). The efficacy results are presented in the table below, which was adapted from the prescribing information.

	Fabhalta® (N=62)	Anti-C5[1] (N=35)	Difference; p-value
Primary Endpoints			
Patients with sustained ↑ of hemoglobin levels ≥2g/dL from baseline in the absence of transfusions. Response rate (%)	51/62 (82.3%)	0/35 (0%)	81.5%[2]; p<0.0001
Patients with sustained hemoglobin level ≥12g/dL in the absence of transfusions. Response rate (%)	42/62 (67.7%)	0/35 (0%)	66.6%[2]; p<0.0001
Secondary Endpoints			
Patients avoiding transfusion. Transfusion avoidance rate (%)	59/62 (95.2%)	16/35 (45.7%)	49.5%[2]; p<0.0001
Hemoglobin change from baseline (g/dL), adjusted mean	3.6	-0.1	3.7; p<0.0001
Absolute reticulocyte count change from baseline (10^9/L), adjusted mean	-116	0	-116; p<0.0001

[1] eculizumab or ravulizumab [2]Adjusted difference in proportion

Study APPOINT-PNH is a single arm study that included adults with PNH who were not previously treated with a complement inhibitor. This study included adults with PNH (N=40), a hemoglobin <10g/dL, and LDH>1.5 times upper limit of normal (ULN) who were treated with Fabhalta® 200mg PO BID 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.

The mean age of included patients was 42.1 years, while 42.5% were female and the mean disease duration was 4.7 years. The baseline mean PNH RBC clone size (Type II + III) was 42.7%, mean baseline hemoglobin was 8.2g/dL, and about 70% of patients required a transfusion in the 6 months prior to treatment. The baseline mean LDH level was 1,699 U/L, and the mean absolute reticulocyte count was 154 X 10^9/L. Approximately 13% of patients had a history

of major adverse vascular events (MAVEs), and no patients discontinued from the core treatment period of the study.

In total, 77.5% of patients (31/40) achieved a sustained increase (between day 126 and day 168) in hemoglobin levels from baseline of ≥2g/dL in the absence of RBC transfusions, based on central laboratory hemoglobin values. In a sensitivity analysis, 87.5% of patients (35/40) achieved a sustained increased (between day 126 and day 168) in hemoglobin levels from baseline of ≥2g/dL in the absence of RBC transfusions, including local laboratory hemoglobin values when central laboratory hemoglobin values were not available.

Place in Therapy: Fabhalta®, a complement factor B inhibitor, is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). It has a box warning regarding serious infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type B. Complete or update vaccination for encapsulated bacteria at least 2 weeks prior to the first dose of Fabhalta®, unless the risks of delaying therapy with Fabhalta® outweigh the risk of developing a serious infection. Due to the risk of serious infections, Fabhalta® is available only through a restricted program under a REMS called the Fabhalta® REMS.

The efficacy of Fabhalta® was assessed in an open-label, active comparator-controlled study that included adults with PNH and residual anemia despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization. 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 a sustained increase of ≥2g/dL in hemoglobin levels from baseline (hemoglobin improvement), as well as sustained hemoglobin levels ≥12g/dL. Results suggested that Fabhalta® was statistically significantly more effective than anti-C5 treatment for the primary endpoints, as well as the various secondary endpoints assessed.

Fabhalta® is the first oral monotherapy FDA approved for adults with PNH, and is approved for use in previously-treated and treatment-naïve patients. Ravulizumab (brand name Ultomiris®) is an IV infusion indicated for the treatment of adult and pediatric patients one month of age and older with PNH, while eculizumab (brand name Soliris®) is an IV infusion indicated for the treatment of adult patients with PNH to reduce hemolysis. Ultomiris® and Soliris® were used as the active-comparator in the treatment-experienced patients with PNH study (APPLY-PNH).

There is some evidence in a phase 3 study to suggest Fabhalta® may be more effective than anti-C5 treatment (eculizumab or ravulizumab) for the primary endpoints of proportion of patients demonstrating sustained increase of ≥2g/dL in hemoglobin levels from baseline and sustained hemoglobin levels ≥12g/dL. It is recommended that Fabhalta® remain non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Fabhalta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2023.
[2] Ultomiris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc; 2022.
[3] Soliris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc; 2020.