Fabhalta® (iptacopan)

About Fabhalta in paroxysmal nocturnal hemoglobinuria (PNH)

Fabhalta® (iptacopan) is the first oral monotherapy for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH),[1] a rare, chronic, and serious complement-mediated blood disorder.[2]

Fabhalta is a Factor B inhibitor that acts proximally in the alternative complement pathway of the immune system, providing comprehensive control of red blood cell (RBC) destruction within and outside the blood vessels, mostly in the liver and spleen (intra- and extravascular hemolysis [IVH and EVH]).[1]

Patients with PNH may need lifelong treatment and some may need interventions, such as blood transfusions, to manage complications of their illness.[3-7]

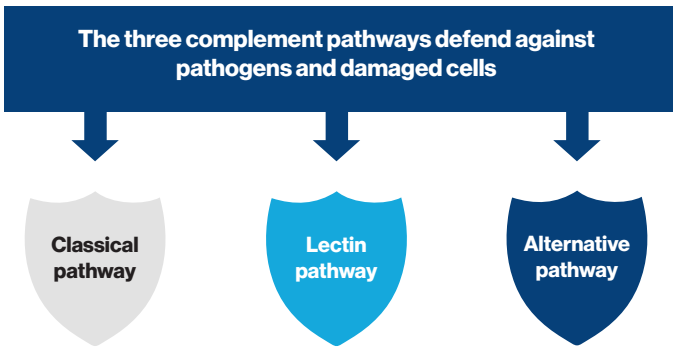
The complement system and PNH

The **complement system** is a key part of the body's **innate immune system** that acts as part of the first line of defense against infections.[8-9]

It consists of three pathways – **classical, lectin, and alternative**.[8-9]

Each pathway can become activated to trigger a cascade of protein reactions that initiate an immune response to detect and eliminate pathogens.[8-9]

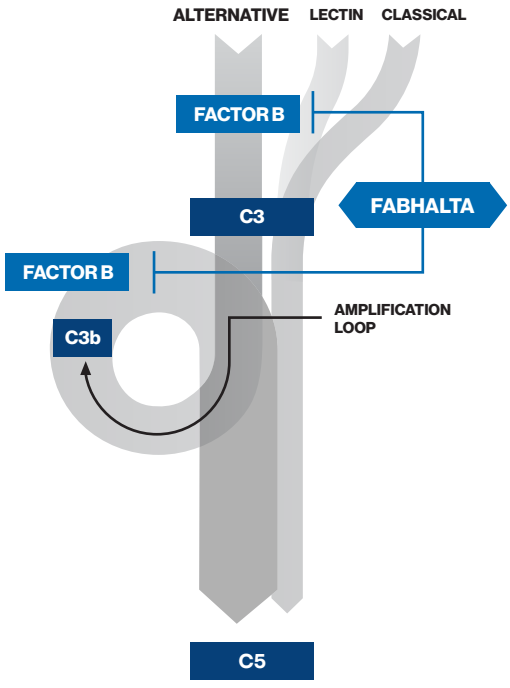
The **alternative pathway** acts as an amplification loop of the other two pathways, which is triggered by the activation of multiple proteins, including **Factor B**.[10]



When the complement system is overactive, or mistakenly attacks healthy parts of the body, it can cause a number of diseases known as **complement-mediated diseases, or CMDs**, such as PNH.[9]

How Fabhalta works in PNH

Fabhalta is a Factor B inhibitor that acts proximally in the alternative pathway of the complement system.[1]



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The FDA approval of Fabhalta is based on the Phase 3 APPLY-PNH trial in patients with residual anemia (hemoglobin < 10 g/dL) despite prior anti-C5 treatment who switched to Fabhalta, which demonstrated superiority in hemoglobin (Hb) improvement in the absence of RBC transfusions and in transfusion avoidance rate over patients who stayed on anti-C5 treatments.[1,11] Approval was also supported by the Phase 3 APPOINT-PNH study in complement inhibitor-naïve patients.[1,11-12]

The **APPLY-PNH** trial (N=97) demonstrated that Fabhalta was superior to anti-C5 treatments in improving Hb levels for patients with PNH with residual anemia (Hb <10 g/dL) who were on prior anti-C5 treatment:[11]

Proportion of patients whose Hb levels in the absence of RBC transfusions increased by ≥2 g/dL[a] from baseline without RBC transfusions* after 24 weeks of treatment

82.3%
of patients who switched to **Fabhalta**
N=51/62

vs

0%
of patients who continued on **anti-C5**
(difference of 81.5%[b], P<0.0001)
N=0/35

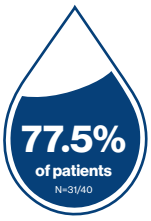
Proportion of patients who achieved Hb levels of ≥12 g/dL without RBC transfusions* after 24 weeks of treatment

67.7%
of patients who switched to **Fabhalta**
N=42/62

vs

0%
of patients who continued on **anti-C5**
(difference of 66.6%[b], P<0.0001)
N=0/35

In the **APPOINT-PNH** trial (N=40), where Fabhalta was studied in patients with PNH who had never been treated with a complement inhibitor before, the majority of patients achieved an increase in their Hb levels of ≥2 g/dL[a] from baseline without RBC transfusions*:[12]



77.5% of patients had a sustained increase in their Hb levels of ≥2 g/dL from baseline[a] without RBC transfusions* with **Fabhalta**

[a]Assessed between Days 126 and 168. [b]Adjusted difference in proportion.
*Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.

APPLY-PNH and APPOINT-PNH demonstrated Fabhalta's safety profile in patients with PNH.[11,12]

In the APPLY-PNH trial, the most commonly reported (≥10%) adverse reactions (ARs) with Fabhalta vs. anti-C5s were: headache (19% vs. 3%), nasopharyngitis (16% vs. 17%), diarrhea (15% vs. 6%), abdominal pain (15% vs. 3%), bacterial infection (11% vs. 11%), nausea (10% vs. 3%), and viral infection (10% vs. 31%).[11] In the APPOINT-PNH trial, the most commonly reported ARs (≥10%) were headache (28%), viral infection (18%), nasopharyngitis (15%), and rash (10%).[12]

In APPLY-PNH, serious adverse reactions were reported in two (3%) patients with PNH receiving Fabhalta and included pyelonephritis, urinary tract infection and COVID-19.[11] In APPOINT-PNH, serious adverse reactions were reported in two (5%) patients with PNH receiving Fabhalta and included COVID-19 and bacterial pneumonia.[12]

Fabhalta may cause serious infections caused by encapsulated bacteria and is available only through a Risk Evaluation and Mitigation Strategy (REMS) that requires vaccination for encapsulated bacteria.

Clinical development of Fabhalta for PNH and other CMDs

Fabhalta has received FDA approval for the treatment of adults with PNH.[1]

Fabhalta is also currently in development for a number of other CMDs where significant unmet needs exist.

Indication

FABHALTA is a prescription medicine used to treat adults with paroxysmal nocturnal hemoglobinuria (PNH).

It is not known if FABHALTA is safe and effective in children.

Important Safety Information

FABHALTA is a medicine that affects part of the immune system and may lower one's ability to fight infections. FABHALTA increases the chance of getting serious infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type B. These serious infections may quickly become life-threatening or fatal if not recognized and treated early. Patients must complete or update vaccinations against these bacteria at least 2 weeks before starting FABHALTA. If patients have not completed these vaccinations and FABHALTA therapy must be started right away, they should receive the required vaccinations as soon as possible. If patients have not been vaccinated and FABHALTA must be started right away, they should also receive antibiotics to take for as long as their doctor tells them. If patients have been vaccinated against these bacteria in the past, they might need additional vaccinations before starting FABHALTA. Their doctor will decide if they need additional vaccinations. Vaccines do not prevent all infections caused by encapsulated bacteria. Patients should call their doctor or get emergency medical care right away if they have any of these signs and symptoms of a serious infection: fever with or without shivers or chills; fever with chest pain and cough; fever with high heart rate; headache and fever; confusion; clammy skin; fever and a rash; fever with breathlessness/fast breathing; headache with nausea or vomiting; headache with stiff neck or stiff back; body aches with flu-like symptoms; or eyes sensitive to light. Doctors will give their patients a Patient Safety Card about the risk of serious infections. Patients must carry it with them at all times during treatment and for 2 weeks after their last dose of FABHALTA. The risk of serious infections may continue for a few weeks after their last dose of FABHALTA. It is important for patients to show this card to any doctor who treats them. This will help doctors diagnose and treat patients quickly.

FABHALTA is only available through a program called the FABHALTA Risk Evaluation and Mitigation Strategy (REMS). Before patients can take FABHALTA, their doctor must enroll in the FABHALTA REMS program, counsel patients about the risk of serious infections caused by certain bacteria, give patients information about the symptoms of serious infections, make sure that patients are vaccinated against serious infections caused by encapsulated bacteria and that they receive antibiotics if they need to start FABHALTA right away and are not up to date on vaccinations, as well as give patients a Patient Safety Card about the risk of serious infections.

Since FABHALTA may increase patients' cholesterol and triglycerides, their doctor will do blood tests to check their levels periodically.

Patients should not take FABHALTA if they are allergic to FABHALTA or any of the ingredients in FABHALTA. Patients should not take FABHALTA if they have a serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis,* or *Haemophilus influenzae* type B when starting FABHALTA.

Before taking FABHALTA, patients should tell their doctor about all their medical conditions, including if they have an infection or fever, have kidney or liver problems, are pregnant or plan to become pregnant (it is not known if FABHALTA will harm an unborn baby), or are breastfeeding or plan to breastfeed as it is not known if FABHALTA passes into breast milk. Patients should not breastfeed during treatment and for 5 days after the last dose of FABHALTA.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking FABHALTA with certain other medicines may affect the way FABHALTA works and may cause side effects. Patients should know the medicines they take and the vaccines they receive. Patients should keep a list of them to show their doctor and pharmacist when they get a new medicine.

If patients have PNH and stop taking FABHALTA, their doctor will need to monitor them closely for at least 2 weeks after stopping FABHALTA. Stopping treatment with FABHALTA may cause a breakdown of red blood cells due to PNH. Symptoms or problems that can happen due to breakdown of red blood cells include decreased hemoglobin level in the blood; blood in the urine; shortness of breath; trouble swallowing; tiredness; pain in the stomach (abdomen); blood clots, stroke, and heart attack; and erectile dysfunction (ED). It is important that patients take FABHALTA exactly as their doctor tells them to lower the possibility of breakdown of red blood cells due to PNH.

The most common side effects of FABHALTA include headache; nasal congestion, runny nose, cough, sneezing, and sore throat (nasopharyngitis); diarrhea; pain in the stomach (abdomen); infections (viral and bacterial); nausea; and rash.

Please see full Prescribing Information, including Boxed WARNING and Medication Guide.

References

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