## Fabhalta® (iptacopan) – New drug approval

- On December 6, 2023, Novartis announced the FDA approval of Fabhalta (iptacopan), for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

- PNH is a rare and chronic complement-mediated blood disorder. People with PNH have an acquired mutation in some of their hematopoietic stem cells that causes them to produce red blood cells (RBCs) that are susceptible to premature destruction by the complement system.

    - It is estimated that approximately 10 to 20 people per million worldwide live with PNH.

- Fabhalta (iptacopan) is a first-in-class factor B inhibitor of the alternative complement pathway. Fabhalta is the first oral therapy approved for PNH.

- The efficacy of Fabhalta was established in APPLY-PNH, an open-label, active comparator-controlled study in 97 adults with PNH and residual anemia (hemoglobin < 10 g/dL) despite previous treatment with a stable regimen of anti-C5 treatment (either Soliris® [eculizumab] or Ultomiris® [ravulizumab]) for at least 6 months prior to randomization. Patients were randomized to switch to Fabhalta or to continue anti-C5 treatment. 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: 1) sustained increase of ≥ 2 g/dL in hemoglobin levels from baseline and 2) sustained hemoglobin levels ≥ 12 g/dL.

    - A sustained increase in hemoglobin levels was achieved in 82.3% of patients with Fabhalta vs. 0% with anti-C5 treatment (treatment difference 81.5, 95% CI: 71.6, 91.4; p < 0.0001).
    - Patients with sustained hemoglobin level ≥ 12 g/dL were 67.7% with Fabhalta vs. 0% with anti-C5 treatment (treatment different 66.6, 95% CI: 54.6, 78.6; p < 0.0001).

- In addition to APPLY-PNH, Fabhalta was also evaluated in APPOINT-PNH, a single arm study in 40 adults with PNH who were not previously treated with a complement inhibitor.

    - 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 ≥ 2 g/dL in the absence of RBC transfusions.

- Fabhalta carries a boxed warning for serious infections caused by encapsulated bacteria.

    - Fabhalta is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Fabhalta REMS.

- Fabhalta is contraindicated:

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

- Additional warnings and precautions for Fabhalta include monitoring of PNH manifestations after Fabhalta discontinuation and hyperlipidemia.

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- The most common adverse reactions (≥ 10%) with Fabhalta use were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.

- The recommended dose of Fabhalta is 200 mg orally twice daily. To reduce the potential risk of hemolysis with abrupt discontinuation of other PNH therapies:

    — For patients switching from Soliris, Fabhalta should be initiated no later than 1 week after the last dose of Soliris.
    — For patients switching from Ultomiris, Fabhalta should be initiated no later than 6 weeks after the last dose of Ultomiris.
    — There is no available information regarding the timeframe for initiation of Fabhalta after other PNH therapies.

- Novartis plans to launch Fabhalta in December 2023. Fabhalta will be available as a 200 mg capsule

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