Clinical Perspectives

FABHALTA® (iptacopan) 200 mg capsules

FEATURED EXPERTS:

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In this Expert Perspectives newsletter, Dr Lawrence Rice and Dr Ilene Weitz will discuss PNH and review clinical data for FABHALTA.

The perspectives provided within this newsletter by Dr Lawrence Rice and Dr Ilene Weitz are their own and not reflective of their affiliations. The medical experts in this newsletter have been paid by Novartis to provide their perspectives. This newsletter is not intended to be and does not serve as medical advice, guidance, or recommendations from Novartis.

INDICATION

FABHALTA is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

IMPORTANT SAFETY INFORMATION

WARNING: 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 vaccinations 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 evaluate 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.

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Unmet Therapeutic Needs in Patients with PNH

"PNH is a serious and devastating disease with a significant impact on patients. Currently available treatments have been of great benefit to patients. However, extravascular hemolysis can develop with the use of C5 inhibitors.[1] FABHALTA® (iptacopan) offers an efficacious oral treatment option that addresses both intra- and extravascular hemolysis.[2,3]"

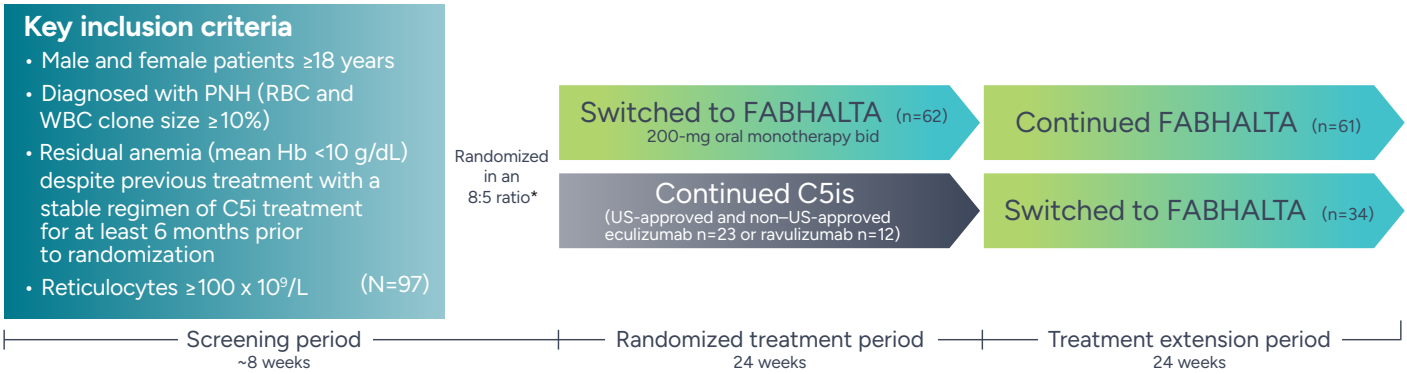
-DR RICE

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired disease characterized by hemolytic anemia, thrombosis, and bone marrow failure.[1,4] FABHALTA represents a novel approach to complement inhibition as a Factor B inhibitor that acts proximally in the alternative pathway of the complement system.[5]

FABHALTA Was Studied in C5i-Experienced Adult Patients with PNH

APPLY, a phase 3, open-label, active comparator-controlled study, evaluated the efficacy and safety of FABHALTA.[3,5] Ninety-seven patients were randomized to switch to FABHALTA 200 mg orally twice daily (n=62) or to continue anti-C5 treatment (n=35) throughout the 24-week randomized treatment period (**Figure 1**).[5] After the randomized treatment period, all patients were eligible to enroll in a 24-week treatment extension period and receive FABHALTA.[5]

Figure 1. APPLY Study Design[3,5,6]



The two primary end points in APPLY were the proportion of patients achieving sustained increase of ≥2 g/dL† in hemoglobin (Hb) levels from baseline without a need for red blood cell (RBC) transfusions‡ after 24 weeks and the proportion of patients achieving sustained Hb levels ≥12 g/dL† without a need for RBC transfusions after 24 weeks.[3,5,‡]

Additional end points included RBC transfusion avoidance§, change from baseline† in: Hb levels‖, scores per the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), absolute reticulocyte count (ARC) (10^9/L), lactate dehydrogenase (LDH) level. The occurrence of major adverse vascular events¶ and occurrence of clinical breakthrough hemolysis were additional end points.[3,5,¶,#]

* Randomization was stratified based on prior C5i treatment and transfusion history within the last 6 months.[5]
† Assessed between Days 126 and 168.[5]
‡ Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[3]
§ Transfusion avoidance is defined as absence of administration of packed-RBC transfusions between Days 14 and 168.[5,7]
‖ Excludes values within 30 days post-transfusion.[3]
¶ Throughout the study.[2,3]
# As per the protocol definition.[2,3]

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

- Patients with serious hypersensitivity to FABHALTA 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.

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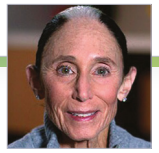
"The APPLY study was a phase 3 study that evaluated the use of FABHALTA in patients who had already received anti-C5 therapy (eculizumab or ravulizumab).[5] The trial included the type of patients I see regularly in clinical practice, which is important to me when considering FABHALTA for my appropriate adult patients."



-DR WEITZ

Select baseline characteristics[5]:

Baseline disease characteristics were generally well balanced between treatment groups.

	Mean age (SD) (years)	Mean (SD) Hb (g/dL)	Mean (SD) LDH (U/L)	Mean (SD) ARC (x 10^9/L)	Mean (SD) disease duration (years)
FABHALTA	51.7 (16.9)	8.9 (0.7)	269 (70) (<1.5 x ULN)	193 (84)	11.9 (9.8)
C5is	49.8 (16.7)	8.9 (0.9)	273 (85) (<1.5 x ULN)	191 (81)	13.5 (10.9)

	Required ≥1 transfusion in last 6 months (% of patients)	Mean (SD) time on prior C5i (years)	Prior C5i treatment on eculizumab (% of patients)	Prior C5i treatment on ravulizumab (% of patients)
FABHALTA	56.5%	3.8 (3.5)	64.5%	35.5%
C5is	60.0%	4.2 (3.9)	65.7%	34.3%

BID, twice daily; SD, standard deviation; ULN, upper limit of normal; WBC, white blood cell.

In the APPLY study analysis:

- All end points were based on central laboratory data[5,7]
- 95% CIs were based on the Sato variance estimator[7]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Serious Infections Caused by Encapsulated Bacteria

- FABHALTA, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis* (caused by any serogroup, including nongroupable strains), and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. The initiation of FABHALTA is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria.

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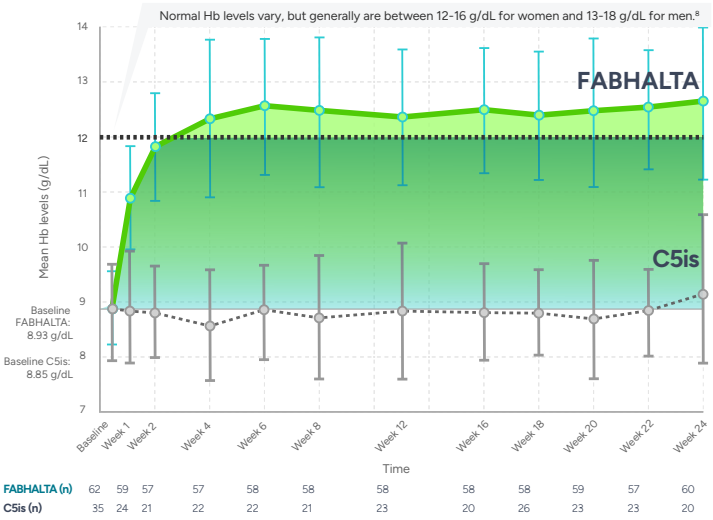
Efficacy in the APPLY Trial

FABHALTA met the two primary end points of APPLY, having achieved superior Hb improvements over C5is (eculizumab or ravulizumab).[5] In fact, significantly more patients achieved Hb improvements in the absence of RBC transfusions with FABHALTA vs C5is.[5] FABHALTA treatment resulted in a response rate of 82.3% (n=51/62; 95% CI, 70.5-90.8) compared to 0% for the C5i group (n=0/35; 95% CI, 0-10.0) (difference*: 81.5%; 95% CI, 71.6-91.4; *P*<0.0001) for sustained Hb increase of ≥2 g/dL† from baseline in the absence of RBC transfusions after 24 weeks.‡

Additionally, the response rate for patients achieving sustained, normalized§ Hb levels of ≥12 g/dL† in the absence of RBC transfusions‡ after 24 weeks was 67.7% for the FABHALTA group (n=42/62; 95% CI, 54.7-79.1) vs 0% in the C5i group (n=0/35; 95% CI, 0-10.0) (difference*: 66.6%; 95% CI, 54.6-78.6; *P*<0.0001).[5]

FABHALTA also provided a substantial Hb increase after the 24-week randomized treatment period. As an additional end point, FABHALTA delivered a +3.6 g/dL adjusted mean change in Hb level from baseline vs -0.1 g/dL with C5is.[5]

Figure 2. Mean Hb levels (g/dL) through Week 24 (values within 30 days of transfusion were excluded and considered missing)[7]



Additional End Point

FABHALTA (n=62)

+3.6 g/dL
(95% CI, 3.3-3.9)
adjusted mean increase in Hb from baseline vs

-0.1 g/dL
with C5is (eculizumab or ravulizumab) (95% CI, -0.5 to 0.3)
(Adjusted mean difference: 3.7 g/dL; 95% CI, 3.2-4.1; *P*<0.0001)[5]

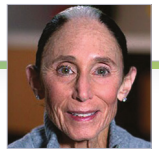
Adjusted mean assessed between Weeks 18 and 24‡

Excludes values within 30 days post-transfusion

The data in the figure above are exploratory, presented for observation only.
No formal conclusions or comparisons between the two treatment arms can be made.

* Adjusted difference in proportion.[5]
† Assessed between Days 126 and 168.[5]
‡ Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[3]
§ Normalization defined as meeting the primary end point of Hb ≥12 g/dL.[3] Normal Hb levels vary, but generally are between 12-16 g/dL for women and 13-18 g/dL for men.[3,8]

"The APPLY trial showed that patients achieved superior Hb improvements with FABHALTA over C5is. It means a lot to my patients that FABHALTA can help them to achieve greater Hb improvements in the absence of RBC transfusions when compared to their past C5is.[3]"



-DR WEITZ

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Serious Infections Caused by Encapsulated Bacteria (continued)

- Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to the start of FABHALTA, according to the current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with FABHALTA. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. The benefits and risks of treatment with FABHALTA, as well as the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by encapsulated bacteria.

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Additional End Point: RBC Transfusion Avoidance

More patients achieved RBC transfusion avoidance with FABHALTA vs C5is (eculizumab or ravulizumab) during the APPLY study (assessed between Weeks 2 and 24).[3,5,*,†]

Response rates

95.2% FABHALTA (n=59/62; 95% CI, 86.5-99.0)	45.7% C5is (n=16/35; 95% CI, 28.8-63.4)
(Difference‡: 49.5%; 95% CI, 32.5-66.6; *P*<0.0001)	

35/62 patients in the FABHALTA arm and 21/35 in the C5i arm had at least 1 RBC transfusion in the 6 months prior to trial enrollment.[5]

* Assessed between Days 14 and 168.[5]
† Transfusion avoidance is defined as absence of administration of packed-RBC transfusions between Days 14 and 168.[5]
‡ Adjusted difference in proportion.[5]

"The APPLY trial is noteworthy in that FABHALTA provided a robust Hb increase during the 24-week randomized treatment period.[3] When combined with the response rate data for transfusion avoidance, FABHALTA makes sense for me to consider in my appropriate adult patients with PNH."

-DR RICE

Additional End Point: The Impact of FABHALTA on ARC and LDH Levels

During APPLY, the adjusted mean change from baseline in ARC (10^9/L) assessed between Weeks 18 and 24 (between Days 126 and 168; values within 30 days after transfusion were included in the analysis).[5] Results demonstrated FABHALTA delivered greater reductions in ARC compared to C5is (eculizumab or ravulizumab), with an adjusted mean change from baseline of -116 x 10^9/L (N=62; 95% CI, -127 to -105) and 0 x 10^9/L (N=35; 95% CI, -13 to 14), respectively. (Adjusted mean difference: -116 x 10^9/L; 95% CI, -132 to -100; *P*<0.0001).[5] The values include post-transfusion data.[7]

No statistically significant difference in LDH was seen between FABHALTA and C5is.[7]

The data from this additional analysis are descriptive in nature, presented for observation only. No formal conclusions or comparisons between the two treatment arms can be made.

The adjusted geometric mean ratio to baseline in LDH assessed between Weeks 18 and 24 (between Days 126 and 168) was also performed. In the FABHALTA arm, the ratio was 0.96, and in the C5i (eculizumab or ravulizumab) arm the ratio was 0.97. The mean (SD) (FABHALTA: 275.2 U/L [117.6]; C5is: 280.7 U/L [128.2]) and median (range) (FABHALTA: 251 U/L [150-859]; C5is: 242 U/L [142-815]) LDH values at Day 168 of the randomized treatment period were <1.5 x ULN.[7]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Serious Infections Caused by Encapsulated Bacteria (continued)

- Vaccination does not eliminate the risk of serious encapsulated bacterial infections, despite development of antibodies following vaccination. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated.

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Safety Profile of FABHALTA in the APPLY Trial

Adverse reactions reported in >5% of adults with PNH treated with FABHALTA in APPLY (24-week treatment period)[5]

ADVERSE REACTIONS	**FABHALTA** (N=62) n (%)	**C5is** (eculizumab or ravulizumab) (N =35) n (%)
Headache[a]	12 (19)	1 (3)
Nasopharyngitis[b]	10 (16)	6 (17)
Diarrhea	9 (15)	2 (6)
Abdominal pain[a]	9 (15)	1 (3)
Bacterial infection[c]	7 (11)	4 (11)
Nausea	6 (10)	1 (3)
Viral infection[d]	6 (10)	11 (31)
Arthralgia	5 (8)	1 (3)
Thrombocytopenia[a]	4 (6)	0
Dizziness	4 (6)	0
Systemic hypertension[a]	4 (6)	0
Lipid disorder[e]	4 (6)	0

[a] Includes similar terms.[5]
[b] Nasopharyngitis contains: rhinitis allergic, upper respiratory tract infection, pharyngitis, rhinitis.[5]
[c] Bacterial infection contains: pyelonephritis, urinary tract infection, bronchitis bacterial, bronchitis hemophilus, cholecystitis, folliculitis, cellulitis, arthritis bacterial, sepsis, klebsiella infection, staphylococcal infection, *Pseudomonas* infection, hordeolum, pneumonia bacterial.[5]
[d] Viral infection contains: COVID-19, herpes zoster, oral herpes, nasal herpes, influenza A virus test positive, influenza.[5]
[e] Lipid disorder contains: dyslipidemia, blood cholesterol increased, low density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia.[5]

- Serious adverse reactions were reported in 2 (3%) patients with PNH who received FABHALTA. They included pyelonephritis, urinary tract infection, and COVID-19
- Rash was reported in 2 patients (3%)
- Of the 37 FABHALTA-treated patients who had normal platelet counts at baseline, 43% experienced any grade thrombocytopenia during the randomized treatment period
- Three FABHALTA-treated patients experienced decreased platelets that worsened to grade ≥3 from baseline (1 patient with normal platelets that worsened to grade 4; 1 patient with baseline grade 1 that worsened to grade 4; and 1 patient with baseline grade 3 that worsened to grade 4)
- **No patient discontinued FABHALTA or C5is due to an adverse reaction during the randomized control period of the trial.** One patient discontinued FABHALTA due to pregnancy[3]

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A Study of FABHALTA in Complement Inhibitor-Naive Adults with PNH

APPOINT, a phase 3, single-arm, open-label, uncontrolled study, evaluated the efficacy and safety of FABHALTA in 40 adult patients with a PNH diagnosis, Hb level <10 g/dL, and LDH >1.5 ULN who were not previously treated with a complement inhibitor. All patients received FABHALTA 200 mg orally twice daily during the 24-week open-label core treatment period. After 24 weeks, patients were eligible to enroll in a 24-week treatment extension period (**Figure 3**).[2,5]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

FABHALTA REMS

- FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria.
- Under the FABHALTA REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risks, signs, and symptoms of serious infections caused by encapsulated bacteria, provide patients with the REMS educational materials, ensure patients are vaccinated against encapsulated bacteria, prescribe antibacterial drug prophylaxis if patients' vaccines status is not up to date and treatment must be started urgently, and provide instructions to always carry the Patient Safety Card during treatment and for 2 weeks following last dose of FABHALTA.
- Further information is available by telephone: 1-833-993-2242 or online at www.FABHALTA-REMS.com.

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Figure 3. APPOINT Trial Design[2,5,6]

The primary end point was proportion of patients achieving a sustained increase of ≥2 g/dL‡ in Hb levels from baseline without a need for RBC transfusions§ after 24 weeks.

Additional end points included proportion of patients with sustained Hb level of ≥12 g/dL‡ without a need for RBC transfusions§, RBC transfusion avoidance‖, change from baseline‡ in: Hb levels (g/dL),¶ FACIT-Fatigue scores, ARC (10^9/L), and LDH level. The occurrence of major adverse vascular events# and clinical breakthrough hemolysis#, were additional end points.[2,5]**

* Confirmed by 2 measurements 2 to 8 weeks apart for patients not receiving an RBC transfusion during screening, or by 1 measurement during the first screening visit for patients receiving an RBC transfusion.[2]
† Confirmed by at least 2 measurements 2 to 8 weeks apart during the screening period.[2]
‡ Assessed between Days 126 and 168.[5]
§ Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[2]
‖ Transfusion avoidance is defined as absence of administration of packed-RBC transfusions between Days 14 and 168.[7]
¶ Excludes values within 30 days post-transfusion.[5]
# Throughout the study.[2]
** As per protocol definition.[2]

In the APPOINT study analysis:

- All additional end points were exploratory[5,7]
- Unless otherwise noted, all end points were based on central laboratory data[5,7]
- 95% CIs were based on the Clopper-Pearson method[7]

Select baseline characteristics for patients enrolled in APPOINT (N=40)[2,5]:

Mean (SD) age (years) **42.1 (15.9)**	**Mean (SD) LDH (U/L)** **1699 (683)** **(6.8 x ULN)**	**Mean (SD) disease duration (years)** **4.7 (5.5)**
Mean (SD) Hb (g/dL) **8.2 (1.1)**	**Mean (SD) ARC (x 10^9/L)** **154 (64)**	**Required ≥1 transfusion in last 6 months (% of patients)** **~70%**

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Monitoring of PNH Manifestations After FABHALTA Discontinuation

- After discontinuing FABHALTA, closely monitor patients for at least 2 weeks after the last dose for signs and symptoms of hemolysis. These signs include elevated lactate dehydrogenase (LDH) levels along with sudden decrease in hemoglobin or PNH clone size, fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (such as thrombosis, stroke, and myocardial infarction), dysphagia, or erectile dysfunction. If discontinuation of FABHALTA is necessary, consider alternative therapy.
- If hemolysis occurs after discontinuation of FABHALTA, consider restarting treatment with FABHALTA, if appropriate, or initiating another treatment for PNH.

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Efficacy of FABHALTA in the APPOINT Trial

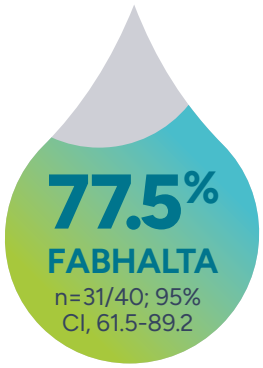
The majority of patients taking FABHALTA experienced Hb improvements in the absence of RBC transfusions[5]

PRIMARY END POINT

Patients with sustained

Hb increase

of ≥2 g/dL* from baseline in the absence of RBC transfusions§ assessed after 24 weeks[5]



Response rate
Based on central laboratory Hb values.

Sensitivity analysis:

87.5%
(n=35/40; 95% CI, 73.2-95.8)

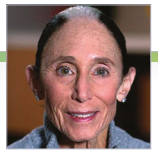
Response rate based on the inclusion of local laboratory values when central laboratory values were not available

FABHALTA is the first PNH treatment to evaluate a primary end point of the response rate of patients achieving sustained Hb increase of ≥2 g/dL, as opposed to Hb stabilization[5,9-11]

Higher Hb levels in the absence of RBC transfusions are within reach[5]

* Assessed between Days 126 and 168.[5]
† Assessed between Day 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[2]

"The mean increase in hemoglobin levels of 2 g/dL or more from baseline observed in the APPOINT trial[2] makes me feel comfortable using FABHALTA in my complement inhibitor-naive patients with PNH. It is important to recognize how such an improvement in hemoglobin levels might benefit patients struggling with PNH."



-DR WEITZ

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hyperlipidemia

- FABHALTA may increase total cholesterol, LDL cholesterol, and serum triglycerides.
- Of 88 FABHALTA-treated patients who had normal total cholesterol at baseline, 31 developed grade 1 hypercholesterolemia during the randomization or core treatment period and 1 patient worsened from baseline grade 1 to grade 2.

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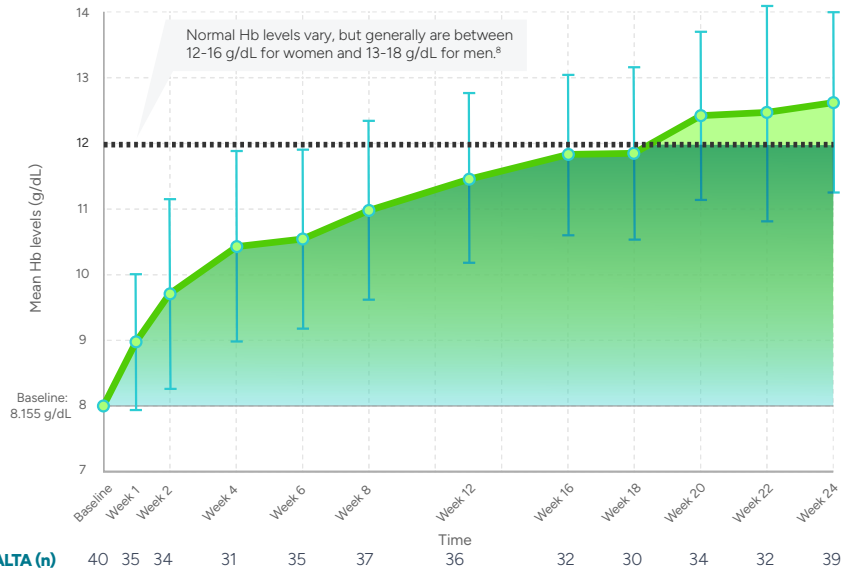
Patients taking FABHALTA experienced an increase in adjusted mean Hb level of +4.29 g/dL from baseline[7]

The data from this additional analysis are exploratory; therefore, not subject to family-wise Type 1 error control, and presented for observation only. No formal conclusions can be made.

Patients experienced increases in mean Hb by Week 1, with increases through Week 24[12]

Figure 4. Mean Hb levels (g/dL) through Week 24 (values within 30 days of transfusion are excluded and considered missing)



FABHALTA (N=40)

+4.29 g/dL
(95% CI, 3.86-4.72)
adjusted mean change in Hb from baseline[7]

Adjusted mean assessed between Weeks 18 and 24*; excludes values within 30 days post-transfusion

Sustained Hb level of ≥12 g/dL* in the absence of RBC transfusions† after 24 weeks was observed in 47.5% of patients (n=19/40; 95% CI, 31.5-63.9)[7]

* Assessed between Days 126 and 168.[5]
† Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[2]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hyperlipidemia (continued)

- Of 96 FABHALTA-treated patients with LDL cholesterol ≤ 130 mg/dL at baseline during the randomization or core treatment period, 14 patients developed LDL cholesterol > 130-160 mg/dL, 6 patients developed LDL cholesterol > 160-190 mg/dL and 4 patients developed LDL cholesterol > 190 mg/dL.
- Of 89 FABHALTA-treated patients with normal triglycerides during the randomization or core treatment period, 22 patients developed grade 1 elevated triglycerides. Three patients experienced an increase in triglycerides from grade 1 to grade 2.
- Of the 102 FABHALTA-treated patients in APPLY-PNH and APPOINT-PNH, 2 patients required cholesterol-lowering medications.
- Monitor serum lipid parameters periodically during treatment with FABHALTA and initiate cholesterol-lowering medications, if indicated.

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ADDITIONAL END POINT

The data from this additional analysis are exploratory; therefore, not subject to family-wise Type 1 error control, and presented for observation only. No formal conclusions can be made.

Patients achieving

RBC transfusion avoidance

assessed between Weeks 2 and 24[7]

Response rate

100%

FABHALTA

(n=40/40; 95% CI, 91.2-100.0) of patients on FABHALTA avoided transfusions

In the 6 months before trial enrollment,

70%

(n=28/40) of patients required a transfusion.[2]

Transfusion avoidance in APPOINT was defined as absence of administration of packed-RBC transfusions between Days 14 and 168.[7]

Additional End Point: The Impact of FABHALTA on LDH and ARC Levels

The data from these additional analyses are exploratory; therefore, not subject to family-wise Type 1 error control, and presented for observation only. No formal conclusions can be made.

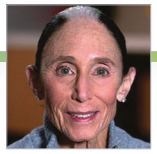
ARC and LDH are 2 of the known biomarkers of hemolytic activity. ARC is a marker of both IVH and EVH, while LDH primarily reflects IVH.[13-15]

During the APPOINT trial, the adjusted mean change from baseline[§] in ARC was -80.75 x 10^9/L (N=40; 95% CI, -87.78 to -73.71). This change was observed with a baseline mean of 154.3 x 10^9/L.[2,7]

With FABHALTA, patients experienced an -83.5% adjusted mean change from baseline[§] in LDH (N=40; 95% CI, -84.9 to -82.0). This change was observed with a baseline mean of 1698.8 U/L. The mean LDH values decreased by Week 1[‖], reached <1.5 x ULN by Week 2[¶], and stayed <1.5 x ULN through Week 24.[2,7,#]

§ Mean of visits between Days 126 and 168.[2]
‖ Day 7.[2]
¶ Day 14.[2]
# Day 168.[2]

"The APPOINT trial looked at a number of additional end points. One of the most important for me was transfusion avoidance. Although no formal conclusions can be drawn from this exploratory data, the response rate of patients who avoided transfusions was 100%.[2]"



-DR WEITZ

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

- The most common adverse reactions (≥10%) in adults with PNH receiving FABHALTA were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.

DRUG INTERACTIONS

- Concomitant use of CYP2C8 inducers (eg, 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 (eg, gemfibrozil) may increase iptacopan exposure, which may result in increased risk for adverse reactions with FABHALTA. Coadministration with a strong CYP2C8 inhibitor is not recommended.

Please click here for full Important Safety Information. Please see accompanying full Prescribing Information, including Boxed WARNING and Medication Guide.

FABHALTA® (iptacopan) 200 mg capsules

Safety Profile of FABHALTA in the APPOINT Trial

Adverse reactions reported in >5% of adults with PNH treated with FABHALTA in APPOINT (24-week treatment period)[2]

ADVERSE REACTIONS	FABHALTA (N=40) n (%)
Headache[a]	11 (28)
Viral infection[b]	7 (18)
Nasopharyngitis[c]	6 (15)
Rash[d]	4 (10)
Abdominal pain[a]	3 (8)
Diarrhea	3 (8)
Lipid disorder[e]	3 (8)

Serious adverse reactions were reported in 2 (5%) patients with PNH who received FABHALTA. They included COVID-19 and bacterial pneumonia.[5]

Bacterial infection[f] and nausea were reported in 2 patients each (5%). Dizziness and urticaria were reported in 1 patient each (3%).[5]

No patient discontinued FABHALTA due to an adverse reaction in the core treatment period of the APPOINT trial.[2]

[a] Includes similar terms.[5]
[b] Viral infection contains: COVID-19, herpes zoster, oral herpes, nasal herpes, influenza A virus test positive, influenza.[5]
[c] Nasopharyngitis contains: rhinitis allergic, upper respiratory tract infection, pharyngitis, rhinitis.[5]
[d] Rash contains: dermatitis allergic, acne, erythema multiforme, rash maculo-papular, rash erythematous.[5]
[e] Lipid disorder contains: dyslipidemia, blood cholesterol increased, low density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia.[5]
[f] Bacterial infection contains: pyleonephritis, urinary tract infection, bronchitis bacterial, bronchitis hemophilus, cholecystitis, folliculitis, cellulitis, arthritis bacterial, sepsis, klebsiella infection, staphylococcal infection, *Pseudomonas* infection, hordeolum, pneumonia bacteria.[5]

"In my practice, I make sure that all patients undergo the required vaccinations per the label[5] before starting therapy to help mitigate the risk of infections due to encapsulated bacteria."

-DR RICE

IMPORTANT SAFETY INFORMATION (continued)

USE IN SPECIFIC POPULATIONS

- Because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.
- FABHALTA is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

Please click here for full Important Safety Information. Please see accompanying full Prescribing Information, including Boxed WARNING and Medication Guide.

FABHALTA® (iptacopan) 200 mg capsules

Help your patients start their journey with FABHALTA

Get your patients started on FABHALTA with these 3 steps[5]

1 Get REMS certified to prescribe FABHALTA

Because of the risk of serious infections caused by encapsulated bacteria, you will need to become certified in the FABHALTA REMS and fulfill its requirements.

To enroll in the REMS:

Review the FABHALTA Prescribing Information and REMS materials.

Submit the completed Prescriber Enrollment form to the FABHALTA REMS at www.FABHALTA-REMS.com, or by fax to 1-877-206-3255.

After enrollment:

Counsel patients about the risk of serious infections caused by encapsulated bacteria, the need for vaccinations, and the early signs and symptoms of serious infections.

Provide patients with REMS educational materials and the Patient Safety Card. Instruct patients to always carry this card with them during treatment and for 2 weeks following the last dose of FABHALTA.

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.

Additional information is available by telephone at 1-833-99FABHA or online at www.FABHALTA-REMS.com.

2 Complete or update vaccinations before starting treatment with FABHALTA

Comply with the most current ACIP recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor.

Required vaccinations:

- *Streptococcus pneumoniae*
- *Neisseria meningitidis* (serogroups A, C, W, Y and B)

Complete or update vaccinations for encapsulated bacteria at least 2 weeks prior to starting FABHALTA, unless the risks of delaying FABHALTA outweigh the risk of developing a serious infection.

- If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. For additional details on antibacterial drug prophylaxis, please see the FABHALTA Prescribing Information, Warning and Precautions (Section 5.1)

During treatment with FABHALTA:

As vaccination does not eliminate the risk of serious encapsulated bacterial infections, closely monitor patients for early signs and symptoms. Inform patients of these signs and symptoms, and instruct patients to seek immediate medical care if they occur.

- Evaluate and treat immediately if infection is suspected, as serious infection may rapidly become life-threatening or fatal if not recognized and treated early. Promptly treat known infections
- Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated
- While on therapy, patients are required to be revaccinated as needed

3 Prescribe FABHALTA through a limited network of specialty pharmacies

Inform your patient which specialty pharmacy will be dispensing their FABHALTA prescription, and tell them to expect a phone call to arrange delivery of their prescription. Pharmacies that dispense FABHALTA must be certified in the FABHALTA REMS and must verify that prescribers are certified.

Onco360®

- Website: onco360.com
- Phone: 1 (877) 662-6633; Fax: 1 (877) 662-6355

Biologics by McKesson

- Website: biologics.mckesson.com
- Phone: 1 (800) 850-4306; Fax: 1 (800) 823-4506

For more information on how to get your patients started on FABHALTA, please visit fabhalta-hcp.com/pnh

Please click here for full Important Safety Information. Please see accompanying full Prescribing Information, including Boxed WARNING and Medication Guide.

FABHALTA® (iptacopan) 200 mg capsules

INDICATION

FABHALTA is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

IMPORTANT SAFETY INFORMATION

WARNING: 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 vaccinations 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 evaluate 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.

CONTRAINDICATIONS

- Patients with serious hypersensitivity to FABHALTA 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.

WARNINGS AND PRECAUTIONS

Serious Infections Caused by Encapsulated Bacteria

- FABHALTA, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis* (caused by any serogroup, including nongroupable strains), and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. The initiation of FABHALTA is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria.
- Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to the start of FABHALTA, according to the current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with FABHALTA. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. The benefits and risks of treatment with FABHALTA, as well as the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by encapsulated bacteria.
- Vaccination does not eliminate the risk of serious encapsulated bacterial infections, despite development of antibodies following vaccination. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated.

FABHALTA REMS

- FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria.
- Under the FABHALTA REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risks, signs, and symptoms of serious infections caused by encapsulated bacteria, provide patients with the REMS educational materials, ensure patients are vaccinated against encapsulated bacteria, prescribe antibacterial drug prophylaxis if patients' vaccine status is not up to date and treatment must be started urgently, and provide instructions to always carry the Patient Safety Card during treatment and for 2 weeks following last dose of FABHALTA.
- Further information is available by telephone: 1-833-993-2242 or online at www.FABHALTA-REMS.com.

Please click here for additional Important Safety Information. Please see accompanying full Prescribing Information, including Boxed WARNING and Medication Guide.

FABHALTA® (iptacopan) 200 mg capsules

WARNINGS AND PRECAUTIONS (continued)

Monitoring of PNH Manifestations After FABHALTA Discontinuation

- After discontinuing FABHALTA, closely monitor patients for at least 2 weeks after the last dose for signs and symptoms of hemolysis. These signs include elevated lactate dehydrogenase (LDH) levels along with sudden decrease in hemoglobin or PNH clone size, fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (such as thrombosis, stroke, and myocardial infarction), dysphagia, or erectile dysfunction. If discontinuation of FABHALTA is necessary, consider alternative therapy.
- If hemolysis occurs after discontinuation of FABHALTA, consider restarting treatment with FABHALTA, if appropriate, or initiating another treatment for PNH.

Hyperlipidemia

- FABHALTA may increase total cholesterol, LDL cholesterol, and serum triglycerides.
- Of 88 FABHALTA-treated patients who had normal total cholesterol at baseline, 31 developed grade 1 hypercholesterolemia during the randomization or core treatment period and 1 patient worsened from baseline grade 1 to grade 2.
- Of 96 FABHALTA-treated patients with LDL cholesterol ≤ 130 mg/dL at baseline during the randomization or core treatment period, 14 patients developed LDL cholesterol > 130-160 mg/dL, 6 patients developed LDL cholesterol > 160-190 mg/dL and 4 patients developed LDL cholesterol > 190 mg/dL.
- Of 89 FABHALTA-treated patients with normal triglycerides during the randomization or core treatment period, 22 patients developed grade 1 elevated triglycerides. Three patients experienced an increase in triglycerides from grade 1 to grade 2.
- Of the 102 FABHALTA-treated patients in APPLY-PNH and APPOINT-PNH, 2 patients required cholesterol-lowering medications.
- Monitor serum lipid parameters periodically during treatment with FABHALTA and initiate cholesterol-lowering medications, if indicated.

ADVERSE REACTIONS

- The most common adverse reactions (≥10%) in adults with PNH receiving FABHALTA were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.

DRUG INTERACTIONS

- Concomitant use of CYP2C8 inducers (eg, 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 (eg, gemfibrozil) may increase iptacopan exposure, which may result in increased risk for adverse reactions with FABHALTA. Coadministration with a strong CYP2C8 inhibitor is not recommended.

USE IN SPECIFIC POPULATIONS

- Because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.
- FABHALTA is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

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

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FABHALTA® (iptacopan) 200 mg capsules

FABHALTA – A Groundbreaking PNH Treatment[5]

FABHALTA® (iptacopan) 200 mg capsules

In the 24-week APPLY (C5i-experienced* patients: FABHALTA, N=62; C5is [eculizumab or ravulizumab], N=35) and APPOINT (Ci-naive patients: FABHALTA, N=40) trials[5]

GROUNDBREAKING Hb IMPROVEMENT[5]

- **Response rates for sustained Hb improvement of ≥2 g/dL†,‡**
  - **82.3%** (95% CI, 70.5-90.8) **vs 0%** (95% CI, 0-10.0) with C5is in C5i-experienced patients§,‖
  - **77.5%** (95% CI, 61.5-89.2) for Ci-naive patients§
- **Response rates for normalized¶ Hb of ≥12 g/dL†,‡**
  - **67.7%** (95% CI, 54.7-79.1) **vs 0%** (95% CI, 0-10.0) with C5is in C5i-experienced patients§,#

TRANSFUSION AVOIDANCE[5]

- **Response rates for RBC transfusion avoidance (Weeks 2 through 24)**:**
  - **95.2%** (95% CI, 86.5-99.0) **vs 45.7%** (95% CI, 28.8-63.4) with C5is in C5i-experienced patients††,‡‡

FIRST AND ONLY FDA-APPROVED ORAL MONOTHERAPY FOR ADULTS WITH PNH[5]

COMPREHENSIVE HEMOLYSIS CONTROL[5]

FABHALTA is a Factor B inhibitor that acts proximally in the alternative complement pathway to control both C3b-mediated EVH and terminal complement-mediated IVH

MOST COMMON ADVERSE REACTIONS IN PATIENTS TAKING FABHALTA (INCIDENCE ≥10%)[5]

Headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash

* Eculizumab or ravulizumab.
† In the absence of transfusions.[5] Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[2,3]
‡ Assessed between Days 126 and 168.[5]
§ Primary end point.[2,5]
‖ Difference: 81.5; 95% CI, 71.6-91.4, *P*<0.0001. Adjusted difference in proportion.[5]
¶ Normalization defined as meeting the primary end point of Hb ≥ 12 g/dL.[3] Normal Hb levels vary, but generally are between 12-16 g/dL for women and 13-18 g/dL for men.[8]
# Difference: 66.6; 95% CI, 54.6-78.6, *P*<0.0001. Adjusted difference in proportion.[5]
** Transfusion avoidance is defined as absence of administration of packed-RBC transfusions between Days 14 and 168.[5]
†† Additional end point.[5]
‡‡ Difference: 49.5; 95% CI, 32.5-66.6, *P*<0.0001. Adjusted difference in proportion.[5]

INDICATION

FABHALTA is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

IMPORTANT SAFETY INFORMATION

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- **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 evaluate 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.

Please click here for full Important Safety Information. Please see accompanying full Prescribing Information, including Boxed WARNING and Medication Guide.

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