ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

Size 0 pale yellow, opaque hard capsule (21.2 to 22.2 mm) with “LNP200” on the body and “NVR” on the cap, containing white or almost white to pale purplish-pink powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FABHALTA is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

4.2 Posology and method of administration

Posology

The recommended dose is 200 mg taken orally twice daily.

Healthcare professionals should advise patients with PNH about the importance of adherence to the dosing schedule in order to minimise the risk of haemolysis (see section 4.4).

If a dose or doses are missed, the patient should be advised to take one dose as soon as possible (even if it is shortly before the next scheduled dose) and then to resume the regular dosing schedule. Patients with several consecutive missed doses should be monitored for potential signs and symptoms of haemolysis.

PNH is a disease that requires chronic treatment. Discontinuation of this medicinal product is not recommended unless clinically indicated (see section 4.4).

Patients switching from anti-C5 (eculizumab, ravulizumab) or other PNH therapies to iptacopan
To reduce the potential risk of haemolysis with abrupt treatment discontinuation:

- For patients switching from eculizumab, iptacopan should be initiated no later than 1 week after the last dose of eculizumab.
- For patients switching from ravulizumab, iptacopan should be initiated no later than 6 weeks after the last dose of ravulizumab.

Switches from complement inhibitors other than eculizumab and ravulizumab have not been studied.

Special populations
Elderly
No dose adjustment is required for patients 65 years of age and older (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild (estimated glomerular filtration rate [eGFR] between 60 and <90 ml/min) or moderate (eGFR between 30 and <60 ml/min) renal impairment. No data are currently available in patients with severe renal impairment or on dialysis and no dose recommendations can be given (see section 5.2).

Hepatic impairment
The use of iptacopan 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 (see section 5.2).

Paediatric population
The safety and efficacy of iptacopan in children aged below 18 years have not been established. No data are available.

Method of administration

For oral use.

This medicinal product may be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who are not currently vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae*, unless the risk of delaying treatment outweighs the risk of developing an infection from these encapsulated bacteria (see section 4.4).
- Patients with unresolved infection caused by encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* type B, at treatment initiation.

4.4 Special warnings and precautions for use

Serious infections caused by encapsulated bacteria

The use of complement inhibitors, such as iptacopan, may predispose individuals to serious, life-threatening or fatal infections caused by encapsulated bacteria. To reduce the risk of infection, all patients must be vaccinated against encapsulated bacteria, including *Neisseria meningitidis* and *Streptococcus pneumoniae*. It is recommended to vaccinate patients against *Haemophilus influenzae* type B if vaccine is available. Healthcare professionals should refer to local vaccination guideline recommendations.

Vaccines should be administered at least 2 weeks prior to administration of the first dose of iptacopan. If treatment must be initiated prior to vaccination, patients should be vaccinated as soon as possible and provided with antibacterial prophylaxis until 2 weeks after vaccine administration.

If necessary, patients may be revaccinated in accordance with local vaccination guideline recommendations.

Vaccination reduces, but does not eliminate, the risk of serious infection. Serious infection may rapidly become life-threatening or fatal if not recognised and treated early. Patients should be informed of and monitored for early signs and symptoms of serious infection. Patients should be

immediately evaluated and treated if infection is suspected. The use of iptacopan during treatment of serious infection may be considered following an assessment of the risks and benefits (see section 4.8).

PNH laboratory monitoring

Patients with PNH receiving iptacopan should be monitored regularly for signs and symptoms of haemolysis, including measuring lactate dehydrogenase (LDH) levels.

Monitoring of PNH manifestations after treatment discontinuation

If treatment must be discontinued, patients should be closely monitored for signs and symptoms of haemolysis for at least 2 weeks after the last dose. These signs and symptoms include, but are not limited to, elevated LDH levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, dysphagia, erectile dysfunction, or major adverse vascular events (MAVEs), including venous or arterial thrombosis. If treatment discontinuation is necessary, alternative therapy should be considered.

If haemolysis occurs after discontinuation of iptacopan, restarting treatment should be considered.

Co-administration with other medicinal products

Concomitant use of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3 has not been studied clinically; therefore, concomitant use is not recommended due to the potential for reduced efficacy of iptacopan (see section 4.5). If an alternative concomitant medicinal product cannot be identified, patients should be monitored for potential signs and symptoms of haemolysis.

Educational materials

All physicians who intend to prescribe FABHALTA must ensure they have received and are familiar with the physician educational materials. Physicians must explain and discuss the benefits and risks of FABHALTA therapy with the patient and provide them with the patient information pack. The patient should be instructed to seek prompt medical care if they experience any sign or symptom of serious infection or serious haemolysis following treatment discontinuation.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on iptacopan

Strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3
Although concomitant administration of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3, such as rifampicin, has not been studied clinically, concomitant use with iptacopan is not recommended due to the potential for reduced efficacy of iptacopan (see section 4.4).

Effects of iptacopan on other medicinal products

CYP3A4 substrates
In vitro data showed iptacopan has potential for induction of CYP3A4 and may decrease the exposure of sensitive CYP3A4 substrates. The concomitant use of iptacopan and sensitive CYP3A4 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP3A4 substrates is required, especially for those with a narrow therapeutic index (e.g. carbamazepine, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

CYP2C8 substrates
In vitro data showed iptacopan has potential for time-dependent inhibition of CYP2C8 and may increase the exposure of sensitive CYP2C8 substrates, such as repaglinide, dasabuvir or paclitaxel.

The concomitant use of iptacopan and sensitive CYP2C8 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP2C8 substrates is required.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of iptacopan in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures between 2- and 8-fold the human exposure at the maximum recommended human dose (MRHD) (see section 5.3).

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, as well as adverse foetal outcomes, including foetal death and premature delivery.

The use of iptacopan in pregnant women or women planning to become pregnant may only be considered following a careful assessment of the risk and benefits, if necessary.

Breast-feeding

It is unknown whether iptacopan is excreted in human milk. There are no data on the effects of iptacopan on the breast-fed newborn/infant or on milk production.

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from FABHALTA therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of iptacopan on human fertility. Available non-clinical data do not suggest an effect of iptacopan treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

FABHALTA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were upper respiratory tract infection (18.9%), headache (18.3%) and diarrhoea (11.0%). The most commonly reported serious adverse reaction was urinary tract infection (1.2%).

Tabulated list of adverse reactions

Table 1 shows the adverse reactions observed in the clinical studies with iptacopan in patients with PNH. Adverse reactions are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000) or very rare (<1/10 000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

System Organ Class Adverse reaction	Frequency category
Infections and infestations	
Upper respiratory tract infection[1]	Very common
Urinary tract infection[2]	Common
Bronchitis[3]	Common
Pneumonia bacterial	Uncommon
Blood and lymphatic system disorders	
Platelet count decreased	Common
Nervous system disorders	
Headache[4]	Very common
Dizziness	Common
Gastrointestinal disorders	
Diarrhoea	Very common
Abdominal pain[5]	Common
Nausea	Common
Skin and subcutaneous tissue disorders	
Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	
Arthralgia	Common

[1] Upper respiratory tract infection includes preferred terms influenza, nasopharyngitis, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection.
[2] Urinary tract infection includes preferred terms urinary tract infection and cystitis escherichia.
[3] Bronchitis includes preferred terms bronchitis, bronchitis haemophilus and bronchitis bacterial.
[4] Headache includes preferred terms headache and head discomfort.
[5] Abdominal pain includes preferred terms abdominal pain, abdominal pain upper, abdominal tenderness and abdominal discomfort.

Description of selected adverse reactions

Platelet count decreased
Decrease in platelet count events was reported in 12/164 (7%) patients with PNH. Of these, 5 patients had events of mild severity, 5 had moderate events and 2 had severe events. Patients with severe events had concurrent anti-platelet antibodies or idiopathic bone marrow aplasia with pre-existing thrombocytopenia. The events started within the first 2 months of iptacopan treatment in 7/12 patients, and after a longer exposure (111 to 951 days) in 5/12 patients. At the cut-off date, 7 (58%) patients had recovered or events were resolving and iptacopan treatment was continued throughout in all patients.

Infections
In PNH clinical studies 1/164 (0.6%) PNH patients reported serious bacterial pneumonia while receiving treatment with iptacopan; the patient had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B and recovered following treatment with antibiotics while continuing treatment with iptacopan.

Blood cholesterol and blood pressure increases
In patients treated with iptacopan 200 mg twice a day in PNH clinical studies, mean increases from baseline of approximately 0.7 mmol/l were seen at month 6 for total cholesterol and LDL-cholesterol. The mean values remained within the normal ranges. Increases in blood pressure, particularly diastolic blood pressure (DBP), were observed (mean increase 4.7 mmHg at month 6). The mean DBP did not exceed 80 mmHg. Total cholesterol, LDL-C and DBP increases correlated with increases in haemoglobin (improvement in anaemia) in patients with PNH (see section 5.1).

Heart rate decrease
In patients treated with iptacopan 200 mg twice a day in PNH clinical studies, a mean decrease in heart rate of approximately 5 bpm was seen at month 6 (mean of 68 bpm).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

During clinical studies, a few patients took up to 800 mg iptacopan daily and this was well tolerated. In healthy volunteers, the highest dose was 1 200 mg administered as a single dose and this was well tolerated.

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, complement inhibitors, ATC code: L04AJ08

Mechanism of action

Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway. Inhibition of FB in the alternative pathway of the complement cascade prevents the activation of C3 convertase and the subsequent formation of C5 convertase to control both C3-mediated extravascular haemolysis (EVH) and terminal complement-mediated intravascular haemolysis (IVH).

Pharmacodynamic effects

The onset of inhibition of the alternative complement pathway, measured using an *ex vivo* alternative pathway assay, Bb levels (fragment b of Factor B) and plasma levels of C5b-9, was ≤2 hours after a single iptacopan dose in healthy volunteers.

A comparable effect of iptacopan was observed in patients with PNH previously exposed to anti-C5 agents and treatment-naïve patients.

In treatment-naïve PNH patients, iptacopan 200 mg twice daily reduced LDH by >60% compared to baseline after 12 weeks and maintained the effect through to the end of the study.

Cardiac electrophysiology

In a QTc clinical study in healthy volunteers, single supra-therapeutic iptacopan doses up to 1 200 mg (which provided greater than 4-fold exposure of the 200 mg twice daily dose), showed no effect on cardiac repolarisation or QT interval.

Clinical efficacy and safety

The efficacy and safety of iptacopan in adult patients with PNH were evaluated in two multicentre, open-label, 24-week phase III studies: an active comparator-controlled study (APPLY-PNH) and a single-arm study (APPOINT-PNH).

APPLY-PNH: anti-C5 treatment experienced patients with PNH
APPLY-PNH enrolled adult PNH patients (RBC clone size ≥10%) with residual anaemia (haemoglobin <10 g/dl) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomisation.

Patients (N=97) were randomised in 8:5 ratio either to receive iptacopan 200 mg orally twice daily (N=62) or to continue anti-C5 treatment (eculizumab N=23; or ravulizumab N=12) throughout the duration of the 24-week randomised controlled period (RCP). Randomisation was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months.

Demographics and baseline disease characteristics were generally well balanced between treatment groups. At baseline, patients had a mean (standard deviation [SD]) age of 51.7 (16.9) years (range 22-84) and 49.8 (16.7) years (range 20-82) in the iptacopan and anti-C5 groups, respectively and 69% of patients were female in both groups. The mean (SD) haemoglobin was 8.9 (0.7) g/dl and 8.9 (0.9) g/dl, in the iptacopan and anti-C5 group, respectively. Fifty-seven percent (iptacopan group) and 60% (anti-C5 group) of patients received at least one transfusion in the 6 months prior to randomisation. Amongst those, the mean (SD) number of transfusions was 3.1 (2.6) and 4.0 (4.3) in the iptacopan and anti-C5 group, respectively. The mean (SD) LDH level was 269.1 (70.1) U/l in the iptacopan group and 272.7 (84.8) U/l in the anti-C5 group. The mean (SD) absolute reticulocyte count was 193.2 (83.6) 10^9/l in the iptacopan group and 190.6 (80.9) 10^9/l in the anti-C5 group. The mean (SD) total PNH RBC clone size (Type II + III) was 64.6% (27.5%) in the iptacopan group and 57.4% (29.7%) in the anti-C5 group.

During the RCP, 1 patient in the iptacopan group discontinued treatment due to pregnancy; no patients in the anti-C5 group discontinued.

Efficacy was based on two primary endpoints to demonstrate superiority of iptacopan to anti-C5 in achieving haematological 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 haemoglobin levels from baseline (haemoglobin improvement) and/or 2) sustained haemoglobin levels ≥12 g/dl.

Iptacopan demonstrated superiority to anti-C5 therapy for the two primary endpoints, as well as for several secondary endpoints including transfusion avoidance, changes from baseline in haemoglobin levels, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, absolute reticulocyte counts (ARCs) and annualised rate of clinical breakthrough haemolysis (see Table 2).

The treatment effect of iptacopan on haemoglobin was seen as early as day 7 and sustained during the study (see Figure 1).

Table 2 Efficacy results for the 24-week randomised treatment period in APPLY-PNH

Endpoints	Iptacopan (N=62)	Anti-C5 (N=35)	Difference (95% CI) p-value
Primary endpoints			
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin levels ≥2 g/dl from baseline[a] in the absence of transfusions)	51/60[b]	0/35[b]	
Response rate[c] (%)	82.3	2.0	80.2 (71.2, 87.6) <0.0001
Number of patients achieving sustained haemoglobin level ≥12 g/dl[a] in the absence of transfusions	42/60[b]	0/35[b]	
Response rate[c] (%)	68.8	1.8	67.0 (56.4, 76.9) <0.0001
Secondary endpoints			
Number of patients avoiding transfusion[d,e]	59/62[b]	14/35[b]	
Transfusion avoidance rate[c] (%)	94.8	25.9	68.9 (51.4, 83.9) <0.0001
Haemoglobin level change from baseline (g/dl) (adjusted mean[f])	3.60	-0.06	3.66 (3.20, 4.12) <0.0001
FACIT-Fatigue score change from baseline (adjusted mean[g])	8.59	0.31	8.29 (5.28, 11.29) <0.0001
Clinical breakthrough haemolysis[h,i], % (n/N)	3.2 (2/62)	17.1 (6/35)	
Annualised rate of clinical breakthrough haemolysis	0.07	0.67	RR=0.10 (0.02, 0.61) 0.01
Absolute reticulocyte count change from baseline (10^9/l) (adjusted mean[g])	-115.8	0.3	-116.2 (-132.0, -100.3) <0.0001
LDH ratio to baseline (adjusted geometric mean[g])	0.96	0.98	Ratio = 0.99 (0.89, 1.10) 0.84
MAVEs[h] % (n/N)	1.6 (1/62)	0	
Annualised rate of MAVEs[h]	0.03	0	0.03 (-0.03, 0.10) 0.32

RR: rate ratio; LDH: lactate dehydrogenase; MAVEs: major adverse vascular events

[a,d,h] Assessed between days 126 and 168[(a)], 14 and 168[(d)], 1 and 168[(h)].

[b] Based on observed data among evaluable patients. (In 2 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally. The haematological response was derived using multiple imputation. These patients did not discontinue.)

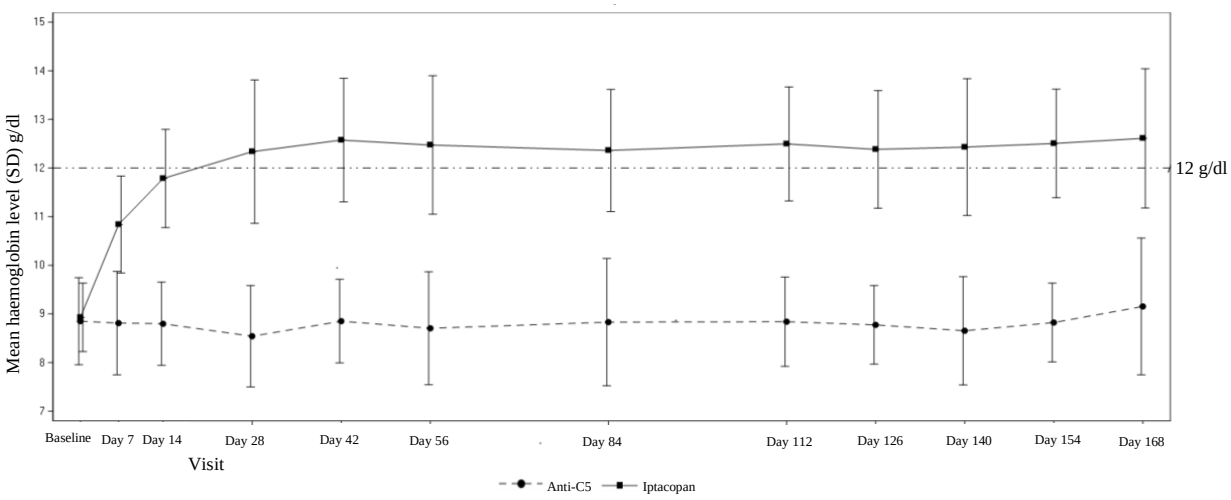
[c] Response rate reflects the model estimated proportion.

[e] Transfusion avoidance is defined as absence of administration of packed red blood cell transfusions between days 14 and 168 or meeting the criteria for transfusion between days 14 and 168.

[f,g] Adjusted mean assessed between days 126 and 168, values within 30 days after transfusion were excluded[(f)]/included[(g)] in the analysis.

[i] Clinical breakthrough haemolysis is defined as meeting clinical criteria (either decrease of haemoglobin level ≥2 g/dl compared to the last assessment or within 15 days, or signs or symptoms of gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH >1.5 x ULN and increased as compared to the last 2 assessments).

Figure 1 Mean haemoglobin level* (g/dl) during 24-week randomised treatment period in APPLY-PNH



*Note: The figure includes all haemoglobin data collected in the study, including those values within 30 days after RBC transfusion.

APPOINT-PNH: Complement inhibitor-naïve study

APPOINT-PNH was a single-arm study in 40 adult PNH patients (RBC clone size ≥10%) with haemoglobin <10 g/dl and LDH >1.5 x ULN who were not previously treated with a complement inhibitor. All 40 patients received iptacopan 200 mg orally twice daily during the 24-week open-label core treatment period.

At baseline, patients had a mean (SD) age of 42.1 (15.9) years (range 18-81) and 43% were female. The mean (SD) haemoglobin was 8.2 (1.1) g/dl. Seventy percent of patients received at least one transfusion in the 6 months prior to treatment. Amongst those the mean (SD) number of transfusions was 3.1 (2.1). The mean (SD) LDH level was 1 698.8 (683.3) U/l, and the mean (SD) absolute reticulocyte count was 154.3 (63.7) 10^9/l. The mean (SD) total PNH RBC clone size (Type II + III) was 42.7% (21.2%). No patients discontinued from the core treatment period of the study.

Efficacy was based on the primary endpoint assessing the effect of iptacopan treatment on the proportion of patients achieving haemoglobin improvement (sustained increase of ≥2 g/dl in haemoglobin levels from baseline, without a need for RBC transfusion, after 24 weeks).

See Table 3 for detailed efficacy results and see Figure 2 for the mean LDH level change during the 24-week core treatment period.

Table 3 Efficacy results for the 24-week core treatment period in APPOINT-PNH

Endpoints	**Iptacopan (N=40) 95% CI**
Primary endpoint	
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin levels ≥2 g/dl from baseline[a] in the absence of transfusions)	31/33[b]
Response rate[c] (%)	92.2 (82.5, 100.0)[d]
Secondary endpoints	
Number of patients achieving sustained haemoglobin level ≥12 g/dl[a] in the absence of transfusions	19/33[b]
Response rate[c] (%)	62.8 (47.5, 77.5)
Number of patients avoiding transfusion[e,f]	40/40[b]
Transfusion avoidance rate[c] (%)	97.6 (92.5, 100.0)
Haemoglobin level change from baseline (g/dl) (adjusted mean[g])	+4.3 (3.9, 4.7)
Clinical breakthrough haemolysis[i,j], % (n/N)	0/40
Annualised rate of clinical breakthrough haemolysis	0.0 (0.0, 0.2)
Absolute reticulocyte count change from baseline (10^9/l) (adjusted mean[h])	-82.5 (-89.3, -75.6)
LDH percent change from baseline (adjusted mean[h])	-83.6 (-84.9, -82.1)
Percentage of patients with MAVEs[j]	0.0

[a,e,j] Assessed between days 126 and 168[(a)], 14 and 168[(e)], 1 and 168[(j)].

[b] Based on observed data among evaluable patients. (In 7 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally. The haematological response was derived using multiple imputation. These patients did not discontinue.)

[c] Response rate reflects the model estimated proportion.

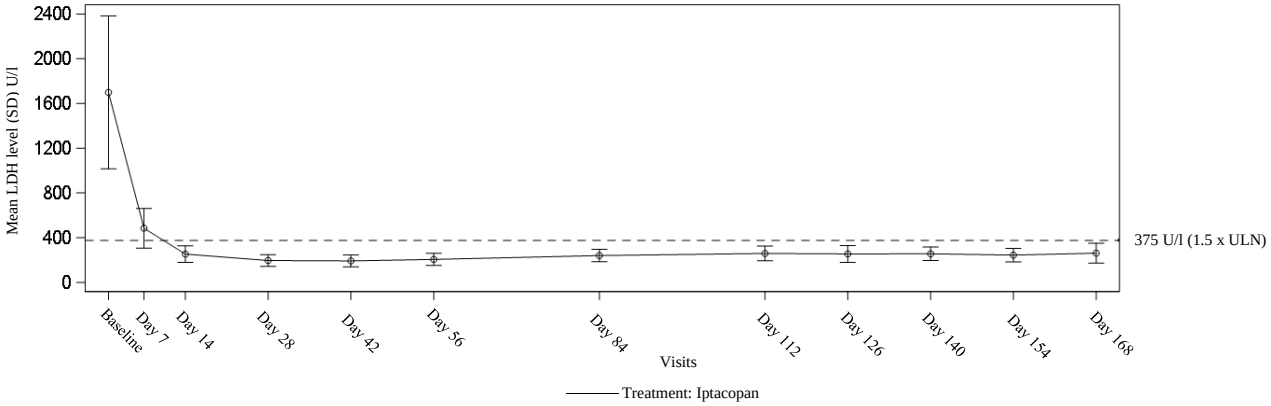
[d] The threshold for demonstration of benefit was 15%, representing the rate that would have been expected on anti-C5 treatment.

[f] Transfusion avoidance is defined as absence of administration of packed red blood cell transfusions between days 14 and 168 or meeting the criteria for transfusion between days 14 and 168.

[g,h] Adjusted mean assessed between days 126 and 168, values within 30 days after transfusion were excluded[(g)]/included[(h)] in the analysis.

[i] Clinical breakthrough haemolysis defined as meeting clinical criteria (either decrease of haemoglobin level ≥2 g/dl compared to the latest assessment or within 15 days; or signs or symptoms of gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH >1.5 x ULN and increased as compared to the last 2 assessments).

Figure 2 Mean LDH level (U/l) during 24-week core treatment period in APPOINT-PNH



Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with FABHALTA in one or more subsets of the paediatric population in PNH (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, iptacopan reached peak plasma concentrations approximately 2 hours post dose. At the recommended dosing regimen of 200 mg twice daily, steady state is achieved in approximately 5 days with minor accumulation (1.4-fold). In healthy volunteers, steady-state $C_{max,ss}$ (geo-mean (%CV)) was 4 020 ng/ml (23.8%) and $AUC_{tau,ss}$ was 25 400 ng*hr/ml (15.2%). Inter- and intra-subject variability in iptacopan pharmacokinetics is low to moderate.

Results from a food-effect study with a high-fat high-calorie meal in healthy volunteers indicated that C_{max} and area under the curve (AUC) of iptacopan were not affected by food. Therefore, iptacopan may be taken with or without food.

Distribution

Iptacopan showed concentration-dependent plasma protein binding due to binding to the target FB in the systemic circulation. Iptacopan was 75 to 93% protein bound *in vitro* at the relevant clinical plasma concentrations. After administration of iptacopan 200 mg twice daily, the geo-mean apparent volume of distribution at steady state was approximately 265 litres.

Biotransformation

Metabolism is a predominant elimination pathway for iptacopan, with approximately 50% of the dose attributed to oxidative pathways. Metabolism of iptacopan includes N-dealkylation, O-deethylation, oxidation and dehydrogenation, mostly driven by CYP2C8 with a small contribution from CYP2D6. Direct glucuronidation (by UGT1A1, UGT1A3 and UGT1A8) is a minor pathway. In plasma, iptacopan was the major component, accounting for 83% of the $AUC_{0\text{-}48\ h}$. Two acyl glucuronides were the only metabolites detected in plasma and were minor, accounting for 8% and 5% of the $AUC_{0\text{-}48\ h}$. Iptacopan metabolites are not considered pharmacologically active.

Elimination

In a study in healthy volunteers, following a single 100 mg oral dose of [^{14}C]-iptacopan, mean total excretion of radioactivity (iptacopan and metabolites) was 71.5% in the faeces and 24.8% in the urine. Specifically, 17.9% of the dose was excreted as parent iptacopan in the urine and 16.8% in faeces. The

apparent clearance (CL/F) after administration of iptacopan 200 mg twice daily at steady state is 7 960 ml/min. The half-life ($t_{½}$) of iptacopan at steady state is approximately 25 hours after administration of iptacopan 200 mg twice daily.

Linearity/non-linearity

At doses between 25 and 100 mg twice daily, the pharmacokinetics of iptacopan were overall less than dose proportional. However, oral doses of 100 mg and 200 mg were approximately dose proportional. Non-linearity was primarily attributed to the saturable binding of iptacopan to its target FB in plasma.

Drug interactions

A dedicated interaction study in which iptacopan was co-administered with other medicinal products was conducted in healthy volunteers and did not demonstrate any clinically relevant interactions.

Iptacopan as a substrate
CYP2C8 inhibitors
When iptacopan is co-administered with clopidogrel (a moderate CYP2C8 inhibitor), the iptacopan C_{max} and the AUC increased by 5% and 36%, respectively.

OATP1B1/OATP1B3 inhibitors
When iptacopan is co-administered with ciclosporin (a strong OATP 1B1/1B3 inhibitor, and a PgP and BCRP inhibitor), the iptacopan C_{max} and AUC increased by 41% and 50%, respectively.

Iptacopan as an inhibitor
PgP substrates
In the presence of iptacopan, the C_{max} of digoxin (a PgP substrate) increased by 8% while its AUC was unchanged.

OATP substrates
In the presence of iptacopan, the C_{max} and AUC of rosuvastatin (an OATP substrate) remained unchanged.

Special populations

A population pharmacokinetic (PK) analysis was conducted on data from 234 patients. Age (18 to 84 years), body weight, eGFR, race and gender did not significantly influence iptacopan PK. Studies that included Asian subjects showed that the PK of iptacopan were similar to Caucasian (white) subjects.

Renal impairment
The effect of renal impairment on the clearance of iptacopan was assessed using a population PK analysis. There were no clinically relevant differences in the clearance of iptacopan between patients with normal renal function and patients with mild (eGFR between 60 and 90 ml/min) or moderate (eGFR between 30 and 60 ml/min) renal impairment and no dose adjustment is required (see section 4.2). Patients with severe renal impairment or on dialysis have not been studied.

Hepatic impairment
Based on a study in subjects with mild (Child-Pugh A, n=8), moderate (Child-Pugh B, n=8) or severe (Child-Pugh C, n=6) hepatic impairment, a negligible effect on the total systemic exposure of iptacopan was observed compared to subjects with normal hepatic function. Unbound iptacopan C_{max} increased 1.4-, 1.7- and 2.1-fold, and unbound iptacopan AUC_{inf} increased by 1.5-, 1.6- and 3.7-fold in subjects with mild, moderate and severe hepatic impairment, respectively (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Reproductive toxicity

In oral dose animal fertility studies, iptacopan did not impact fertility in male rats up to the highest dose tested (750 mg/kg/day), which corresponds to 6-fold the MRHD based on AUC. Reversible effects on the male reproductive system (testicular tubular degeneration and hypospermatogenesis) were observed in repeated dose toxicity studies after oral administration in rats and dogs at doses >3-fold the MRHD based on AUC, with no apparent effects on sperm numbers, morphology or motility, or fertility.

In the female fertility and early embryonic developmental study in rats, iptacopan-related findings were limited to increased pre-and post-implantation losses and, consequently, decreased numbers of live embryos only at the highest dose of 1 000 mg/kg/day orally, which corresponds to ~5-fold the MRHD based on total AUC. The dose of 300 mg/kg/day is the no-observed-adverse-effect level (NOAEL) which corresponds to ~2-fold the MRHD based on AUC.

Animal reproduction studies in rats and rabbits demonstrated that oral administration of iptacopan during organogenesis did not induce adverse embryo or foetal toxicity up to the highest doses, which correspond to 5-fold (for rats) and 8-fold (for rabbits) the MRHD of 200 mg twice daily based on AUC.

In the pre- and postnatal development study in rats, with iptacopan administered orally to females during gestation, parturition and lactation (from gestational day 6 to lactation day 21), there were no adverse effects on pregnant dams or offspring up to the highest dose tested of 1 000 mg/kg/day (estimated 5-fold the MRHD based on AUC).

Repeated dose toxicity

In the chronic toxicity study, one male dog at the highest dose level (margin to clinical exposure near 20-fold), was sacrificed 103 days after completed iptacopan administration due to irreversible non-regenerative severe anaemia associated with bone marrow fibrosis. During the treatment phase, haematology findings indicating inflammation and dyserythropoiesis were observed. No mechanism for the observed findings has been identified and a relation to treatment cannot be excluded.

Mutagenicity and carcinogenicity

Iptacopan was not genotoxic or mutagenic in a battery of *in vitro* and *in vivo* assays.

Carcinogenicity studies conducted with iptacopan in mice and rats via oral administration did not identify any carcinogenic potential. The highest doses of iptacopan studied in mice (1 000 mg/kg/day) and rats (750 mg/kg/day) were approximately 4- and 12-fold the MRHD based on AUC, respectively.

Phototoxicity

In vitro and *in vivo* phototoxicity tests were equivocal. In the *in vivo* phototoxicity study, with iptacopan at doses between 100 and 1 000 mg/kg (equivalent to 38-fold the human total C_{max} at the MRHD), some mice showed a non-dose-response pattern of transient minimal erythema, scabs and dryness and slight increase in average ear weight subsequent to irradiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell

Gelatin
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink

Black iron oxide (E172)
Concentrated ammonia solution (E527)
Potassium hydroxide (E525)
Propylene glycol (E1520)
Shellac (E904)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

FABHALTA is supplied in PVC/PE/PVDC blisters with aluminium foil backing.

Packs containing 28 or 56 hard capsules.
Multipacks containing 168 (3 packs of 56) hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 May 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Pharmaceutical Manufacturing LLC
Verovškova Ulica 57
1000 Ljubljana
Slovenia

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Novartis Farmacéutica S.A.
Gran Via De Les Corts Catalanes 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of FABHALTA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The educational programme is aimed at providing healthcare professionals (HCPs) and patients/caregivers with educational information on the following safety areas of interest:

- Infections caused by encapsulated bacteria
- Serious haemolysis following discontinuation of iptacopan

The MAH shall ensure that in each Member State where FABHALTA is marketed, all HCPs and patients/caregivers who are expected to prescribe or use FABHALTA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals

- **The Guide for healthcare professionals shall contain the following key messages:**
  - FABHALTA may increase the risk of serious infections with encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae.*
  - Ensure patients are vaccinated against *N. meningitidis* and *S. pneumoniae* before starting treatment, and/or receive antibiotic prophylaxis until 2 weeks after vaccination.
  - Recommend vaccination against *H. influenzae* to patients where vaccines are available.
  - Ensure that FABHALTA is only dispensed after a written confirmation that the patient has received vaccination against *N. meningitidis* and *S. pneumoniae*, in accordance with current national vaccination guidelines, and/or is receiving prophylactic antibiotic.
  - Ensure prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis*, *S. pneumoniae*, and, if appropriate, *H. influenzae*)
  - Monitor patients for signs and symptoms of sepsis, meningitis or pneumonia, such as: fever with or without shivers or chills, headache and a fever, fever and a rash, fever with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light. If bacterial infection is suspected, treat with antibiotics immediately.
  - Discontinuation of FABHALTA may increase the risk of serious haemolysis, therefore advice on adherence to the dosing schedule is important, as is close monitoring for signs of haemolysis following treatment discontinuation. If discontinuation of FABHALTA is necessary, alternative therapy should be considered. If haemolysis occurs after discontinuation of FABHALTA, restarting FABHALTA treatment should be considered. Possible signs and symptoms you

need to look out for are: elevated lactate dehydrogenase (LDH) levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, dysphagia, erectile dysfunction or major adverse vascular events including thrombosis.
- Details about the PASS and how to enter patients, if applicable.

The patient information pack:
- Package leaflet
- Patient/caregiver guide
- Patient safety card

- **The Patient/caregiver guide shall contain the following key messages:**
  - Treatment with FABHALTA may increase the risk of serious infections.
  - Doctors will inform you about which vaccinations are required prior to treatment and/or the need to receive antibiotic prophylaxis.
  - Signs and symptoms of serious infection are: fever with or without shivers or chills, headache and a fever, fever and a rash, fever with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light.
  - Contact your doctor in case you experience any of the signs and symptoms above and seek immediate medical care at the nearest medical centre.
  - Discontinuation of FABHALTA may increase the risk of serious breakdown of red blood cells (haemolysis). It is important that you adhere to the scheduled treatment regimen. Possible signs and symptoms you need to look out for are: fatigue, blood in the urine, abdominal pain, shortness of breath, difficulty swallowing, erectile dysfunction or major adverse vascular events including thrombosis.
  - Tell your doctor before discontinuing FABHALTA.
  - If you miss a dose, take it as soon as you can, even if it is close to the next dose.
  - You will receive a patient safety card and will need to carry it with you and tell any treating healthcare professional that you are being treated with FABHALTA.
  - If you have any adverse reactions, including infections or serious haemolysis, it is important that you report them immediately.
  - You will be informed of the details to enroll in the PASS.

- **Patient Safety Card:**
  - Statement that the patient is receiving FABHALTA.
  - Signs and symptoms of serious infection caused by encapsulated bacteria and warning to seek immediate treatment with antibiotics if bacterial infection is suspected.
  - Contact details where a healthcare professional can receive further information.

- **System for Controlled Access:**
  - The MAH shall ensure that in each Member State where FABHALTA is marketed, a system aimed to control access beyond the level of routine risk minimisation measures is in place. The following requirement needs to be fulfilled before the product is dispensed:
  - Submission of written confirmation of the patient's vaccination against *N. meningitidis* and *S. pneumoniae* infections and/or receipt of prophylactic antibiotic according to national guidelines.

- **Annual reminder of mandatory revaccinations:**
  - The MAH shall send to prescribers or pharmacists who prescribe/dispense FABHALTA an annual reminder in order that the prescriber/pharmacist checks if a revaccination (booster vaccination) against *N. meningitidis* and *S. pneumoniae* infections is required for their patients on treatment with FABHALTA, in accordance with current national vaccination guidelines.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF PACK CONTAINING 28 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/001 28 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF PACK CONTAINING 28 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

14 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

'QR code to be included'
www.fabhalta.eu
Scan me

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/001 28 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF PACK CONTAINING 56 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

56 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

'QR code to be included'
www.fabhalta.eu
Scan me

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/002 56 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Multipack: 168 (3 x 56) capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/003 168 (3 x 56) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

56 capsules
Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

'QR code to be included'
www.fabhalta.eu
Scan me

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/003 168 (3 x 56) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg capsules
iptacopan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

FABHALTA 200 mg hard capsules
iptacopan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What FABHALTA is and what it is used for

FABHALTA contains the active substance iptacopan, which belongs to a group of medicines called complement inhibitors.

FABHALTA is used on its own in adults to treat paroxysmal nocturnal haemoglobinuria (PNH), a disease in which the immune system (the body's natural defence system) attacks and damages red blood cells. FABHALTA is used in adults who have anaemia (low levels of red blood cells) due to the breakdown of their red blood cells.

The active substance in FABHALTA, iptacopan, targets a protein called Factor B, which is involved in a part of the body's immune system called the "complement system". In patients with PNH, the complement system is overactive, causing the destruction and breakdown of the red blood cells, which can lead to anaemia, tiredness, difficulty in functioning, pain, pain in the stomach (abdomen), dark urine, shortness of breath, difficulty swallowing, impotence and blood clots. By attaching to and blocking the Factor B protein, iptacopan can stop the complement system from attacking the red blood cells. This medicine has been shown to increase the number of red blood cells and thus may improve symptoms of anaemia.

2. What you need to know before you take FABHALTA

Do not take FABHALTA
- if you are allergic to iptacopan or any of the other ingredients of this medicine (listed in section 6).
- if you have not been vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae*, unless your doctor decides that urgent treatment with FABHALTA is needed.

- if you have an infection caused by a type of bacteria called encapsulated bacteria, including *Neisseria meningitidis, Streptococcus pneumoniae* or *Haemophilus influenzae* type B, before starting FABHALTA treatment.

Warnings and precautions
Serious infection caused by encapsulated bacteria
FABHALTA may increase your risk of infection caused by encapsulated bacteria, including *Neisseria meningitidis* (bacteria that cause meningococcal disease, including serious infection of the linings of the brain and of the blood) and *Streptococcus pneumoniae* (bacteria causing pneumococcal disease, including infection of the lungs, ears and blood).

Talk to your doctor before you start FABHALTA to be sure that you receive vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae*. You may also receive vaccination against *Haemophilus influenzae* type B if this is available in your country. Even if you have had these vaccinations in the past, you might still need to be revaccinated before starting FABHALTA.

These vaccinations should be given at least 2 weeks before starting FABHALTA. If this is not possible, you will be vaccinated as soon as possible after you start FABHALTA and your doctor will prescribe antibiotics for you to use until 2 weeks after you have been vaccinated to reduce the risk of infection.

You should be aware that vaccination reduces the risk of serious infections but may not prevent all serious infections. You should be closely monitored by your doctor for symptoms of infection.

Tell your doctor immediately if you get any of the following symptoms of serious infection during treatment with FABHALTA:
- fever with or without shivers or chills
- headache and a fever
- fever and a rash
- fever with chest pain and cough
- fever with breathlessness/fast breathing
- fever with high heart rate
- headache with feeling sick (nausea) or vomiting
- headache with stiff neck or stiff back
- confusion
- body aches with flu-like symptoms
- clammy skin
- eyes sensitive to light

Children and adolescents
Do not give FABHALTA to children or adolescents below 18 years of age. No data are available on the safety and effectiveness of FABHALTA in this age group.

Other medicines and FABHALTA
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription. In particular:

Tell your doctor or pharmacist if you are using certain medicines because they may stop FABHALTA from working properly:
- certain medicines used to treat bacterial infections – such as rifampicin

Tell your doctor or pharmacist if you are using any of the following medicines because FABHALTA may stop these medicines from working properly:
- certain medicines used to treat epilepsy – such as carbamazepine
- certain medicines used to prevent organ rejection after an organ transplant – such as ciclosporin, sirolimus, tacrolimus
- certain medicines used to treat migraines – such as ergotamine

- certain medicines used to treat chronic pain – such as fentanyl
- certain medicines used to control involuntary movements or sounds – such as pimozide
- certain medicines used to treat an abnormal heart rhythm – such as quinidine
- certain medicines used to treat type 2 diabetes – such as repaglinide
- certain medicines used to treat hepatitis C infection – such as dasabuvir
- certain medicines used to treat cancer – such as paclitaxel

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should also tell your doctor if you become pregnant during treatment with FABHALTA. Your doctor will discuss with you the potential risks of taking FABHALTA during pregnancy or breast-feeding.

Your doctor will decide whether you should take FABHALTA while you are pregnant only after a careful risk-benefit assessment.

It is unkown whether iptacopan, the active substance in FABHALTA, passes into human milk and may affect the breast-fed newborn/infant.

Your doctor will decide whether you should stop breast-feeding or stop FABHALTA treatment, taking into account the benefit of breast-feeding for your baby and the benefit of treatment for yourself.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

3. How to take FABHALTA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Do not exceed the prescribed dose.

The recommended dose is 200 mg (one capsule) to be taken by mouth twice daily (once in the morning and once in the evening). Swallow the FABHALTA capsule with a glass of water.

Taking FABHALTA at the same time each day will help you to remember when to take your medicine.

It is important that you take FABHALTA according to your doctor’s instructions to reduce the risk of breakdown of red blood cells due to PNH.

FABHALTA with food
FABHALTA can be taken with or without food.

Switching from other PNH medicines to FABHALTA
If you are switching from any other PNH medicine, ask your doctor when to start taking FABHALTA.

How long to take FABHALTA
PNH is a lifelong condition and it is expected that you will need to use FABHALTA for a long time. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long you will need to take FABHALTA, talk to your doctor.

If you take more FABHALTA than you should
If you have accidently taken too many capsules or if someone else accidentally takes your medicine, talk to your doctor immediately.

If you forget to take FABHALTA
If you miss a dose or doses, take one dose of FABHALTA as soon as you remember (even if it is shortly before the next scheduled dose), then take the next dose at the usual time. If you miss several doses in a row, contact your doctor who may decide to monitor you for any signs of the breakdown of red blood cells (see section "If you stop taking FABHALTA" below).

If you stop taking FABHALTA
Stopping your treatment with FABHALTA can make your condition worse. Do not stop taking FABHALTA without talking to your doctor first.

If your doctor decides to stop your treatment with this medicine, you will be monitored closely for at least 2 weeks after stopping treatment for any signs of the breakdown of red blood cells. Your doctor may prescribe a different PNH medicine or restart your FABHALTA treatment.

Symptoms or problems that can happen due to breakdown of red blood cells include:
- low levels of haemoglobin in your blood, as seen in blood tests
- tiredness
- blood in the urine
- pain in the stomach (abdomen)
- shortness of breath
- trouble swallowing
- erectile dysfunction (impotence)
- blood clots (thrombosis)

If you experience any of these after stopping treatment, contact your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

The most commonly reported serious side effect is urinary tract infection.

If you experience any of the symptoms of serious infection listed under "Serious infection caused by encapsulated bacteria" in section 2 of this leaflet, you should immediately inform your doctor.

Other side effects

Very common (may affect more than 1 in 10 people)
- infections of the nose and throat (upper respiratory tract infection)
- headache
- diarrhoea

Common (may affect up to 1 in 10 people)
- persistent cough or irritation of the airways (bronchitis)
- low levels of platelets (which help the blood clot) in the blood (thrombocytopenia), which may cause you to bleed or bruise more easily
- dizziness
- pain in the stomach (abdomen)

- feeling sick (nausea)
- joint pain (arthralgia)

Uncommon (may affect up to 1 in 100 people)
- lung infection, which can cause chest pain, cough and fever
- itchy rash (urticaria)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store FABHALTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What FABHALTA contains
- The active substance is iptacopan.
- The other ingredients are:
  - Capsule shell: gelatin, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172)
  - Printing ink: black iron oxide (E172), concentrated ammonia solution (E527), potassium hydroxide (E525), propylene glycol (E1520), Shellac (E904)

What FABHALTA looks like and contents of the pack
Pale yellow, opaque hard capsules, with "LNP200" on the body and "NVR" on the cap, containing white or almost white to pale purplish-pink powder. The capsule size is approximately 21 to 22 mm.

FABHALTA is supplied in PVC/PE/PVDC blisters with aluminium foil backing.

FABHALTA is available in
- packs containing 28 or 56 hard capsules and in
- multipacks comprising 3 cartons, each containing 56 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Pharmaceutical Manufacturing LLC
Verovškova Ulica 57
1000 Ljubljana
Slovenia

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Novartis Farmacéutica S.A.
Gran Via De Les Corts Catalanes 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf.: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.