▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – FABHALTA® (IPTACOPAN) 200 MG HARD CAPSULES

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

Use of FABHALTA may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B, which may become rapidly life-threatening or fatal if not recognised and treated early [see section 4.4, Special Warnings and Precautions for Use].

- **Vaccinate and/or revaccinate according to the current national vaccination guidelines such as the Australian Immunisation Handbook. Vaccines against encapsulated bacteria *Streptococcus pneumoniae* and *Neisseria meningitidis* are required. It is recommended to vaccinate patients against *Haemophilus influenzae* type B.**
- **Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of FABHALTA unless the risks of delaying therapy with FABHALTA outweigh the risk of developing a serious infection. Patients who initiate FABHALTA less than 2 weeks after vaccination must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. See section 4.4, Special Warnings and Precautions for Use for additional guidance on the management of the risk of serious infection.**
- **Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.**

1 NAME OF THE MEDICINE

Iptacopan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg iptacopan (as 225.8 mg iptacopan hydrochloride monohydrate).

List of excipients with known effect: Gelatin may contain residual sulfites

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsule, hard.

Pale yellow opaque, imprinted 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 for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage regimen

The recommended dose is 200 mg taken orally twice daily.

If a dose or doses are missed, the patient should be advised to take one dose of FABHALTA as soon as possible (even if it is soon before the next scheduled dose) and then to resume the regular dosing schedule.

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

Patients switching from anti-C5 (eculizumab, ravulizumab) or other PNH therapies to FABHALTA

To reduce the potential risk of haemolysis with abrupt treatment discontinuation:

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

When switching from other PNH therapies to FABHALTA, the dosing interval and mode of action of the previous medicinal products should be considered.

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

Adherence to dosing schedule

Healthcare providers should advise patients with PNH about the importance of adherence to the dosing schedule in order to minimize the risk of haemolysis (see section 6 Warnings and precautions).

Special populations

Renal impairment

No dose adjustment is required in patients with mild (estimated glomerular filtration rate [eGFR] 60- <90 mL/min/1.73 m^2) or moderate (eGFR 30- <60 mL/min/1.73 m^2) renal impairment (see section 5.2, Pharmacokinetic properties, special populations). No data are currently available in patients with severe renal impairment or on dialysis.

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, Pharmacokinetic properties, special populations).

Paediatric patients

The safety and efficacy of FABHALTA in patients below the age of 18 years have not been established.

Geriatric patients (65 years of age or above)

Limited numbers of patients aged over 65 years were included in the clinical studies, and therefore evidence in this population is limited. No dose adjustment is required for patients aged 65 years and over (see section 5.2, Pharmacokinetic properties, special populations).

Method of administration

For oral use. FABHALTA may be taken with or without food (see section 5.2, Pharmacokinetic Properties).

4.3 CONTRAINDICATIONS

FABHALTA is contraindicated:

- in patients with hypersensitivity to iptacopan or to any of the other excipients.
- in patients who are not currently vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae* unless the risk of delaying FABHALTA treatment outweighs the risk of developing an infection from these encapsulated bacteria (see section 4.4 Special warnings and precautions for use).
- for initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type B.
- for use in combination with other complement inhibitor therapies for PNH, unless medically justified.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious infections caused by encapsulated bacteria

The use of complement inhibitors, such as FABHALTA, 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*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B. Refer to current local vaccination guidelines such as the Australian Immunisation Handbook.

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

If necessary, patients may be revaccinated in accordance with current local vaccination guidelines such as the Australian Immunisation Handbook.

Vaccination reduces, but does not eliminate, the risk of serious infection. Serious infection may rapidly become life-threatening or fatal if not recognized 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.

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 discontinuation of FABHALTA

If treatment with FABHALTA 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 include elevated lactate dehydrogenase (LDH) levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of FABHALTA is necessary, consider alternative therapy.

If haemolysis occurs after discontinuation of FABHALTA, restarting FABHALTA or initiating another treatment for PNH should be considered.

Use in hepatic impairment

See section 5.2, Pharmacokinetic properties, special populations.

Use in renal impairment

See section 5.2, Pharmacokinetic properties, special populations.

Use in the elderly

Limited numbers of patients aged over 65 years were included in the clinical studies, and therefore evidence in this population is limited. No dose adjustment is required for patients aged 65 years and over (see section 5.2, Pharmacokinetic properties, special populations).

Paediatric use

The safety and efficacy of FABHALTA in patients below the age of 18 years have not been established.

Effects on laboratory tests

No data available.

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 Interactions with other medicines and other forms of interactions). 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/caregiver guide and patient safety card. 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro studies indicate that iptacopan does not inhibit common cytochrome P450 enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5) or induce CYP1A2, 2B6, 2C9 or 3A4 at clinically relevant concentrations. Iptacopan also does not inhibit the transporters BCRP, BSEP, MATE1, MATE2-K, MRP2,

OATP1B3, OAT1, OAT3, OCT1 or OCT2 at clinically relevant concentrations *in vitro*. Accordingly, no notable interactions are anticipated in patients. Iptacopan is a substrate for CYP2C8 and for the transporters P-glycoprotein, BCRP, MRP2, OATP1B1 and OATP1B3.

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

- When co-administered with clopidogrel (a moderate CYP2C8 inhibitor), iptacopan C_{max} and AUC increased by 5% and 36%, respectively.
- When co-administered with cyclosporine (a strong OATP 1B1/1B3 inhibitor), iptacopan C_{max} and AUC increased by 41% and 50%, respectively.
- In the presence of iptacopan, the C_{max} of digoxin (a PgP substrate) increased by 8% while its AUC was unchanged.
- In the presence of iptacopan, the C_{max} and AUC of rosuvastatin (an OATP substrate) remained unchanged.

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 Special warnings and precautions for use).

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

Effects on fertility

There are no clinical data on the effect of FABHALTA on fertility.

Iptacopan did not impair fertility in male rats with oral administration up to the highest dose tested (750 mg/kg/day), which corresponds to 19-fold the plasma AUC for unbound drug in patients at the maximum recommended human dose (MRHD) of 200 mg twice daily. Reversible histopathological changes in the male reproductive system (testicular tubular degeneration and cell debris in the lumen of the epididymis) were observed in repeat-dose toxicity studies after oral administration in rats and

dogs at doses ≥10-fold the MRHD based on unbound plasma AUC, with no apparent effects on sperm numbers, morphology or motility.

Iptacopan did not affect fertility in female rats with oral administration up to the highest dose tested (1000 mg/kg/day), yielding exposure 18-fold that of patients at the MRHD (based on plasma AUC for unbound drug). However, this dose did cause adverse effects on early embryonic developmental study (increased pre- and post-implantation losses and, consequently, decreased numbers of live embryos). The dose of 300 mg/kg/day is the no-observed-adverse-effect-level (NOAEL) which corresponds to ~7-fold the MRHD based on plasma AUC for unbound iptacopan.

Use in pregnancy – Category B1

There are insufficient data on FABHALTA use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH in pregnancy. Paroxysmal nocturnal haemoglobinuria in pregnancy is associated with adverse maternal outcomes, including worsening cytopenia, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, as well as adverse fetal outcomes, including fetal death and premature delivery. The use of FABHALTA in pregnant women or women planning to become pregnant may be considered following an assessment of the risks and benefits.

No malformations of other adverse effects on embryofetal development were observed in rats or rabbits with oral administration of iptacopan during the major period of organogenesis up to the highest doses tested (1000 mg/kg/day and 450 mg/kg/day in the respective species). These doses yield exposure to iptacopan 18-times higher in rats (based on unbound plasma AUC) and 8-times higher in rabbits (based on AUC for total drug) than in patients at the MRHD.

Use in lactation

It is not known if iptacopan and/or its metabolites are transferred into milk after oral administration in either humans or animals. There are no data on the effects of FABHALTA on the breast-fed child or on milk production.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for FABHALTA and any potential adverse effects (e.g., serious infections from encapsulated bacteria) on the breast-fed child from FABHALTA or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety profile of FABHALTA is based on analysis of safety data from 102 patients with PNH treated with FABHALTA 200 mg twice daily across two Phase 3 studies (APPLY-PNH and APPOINT-PNH). The median duration of FABHALTA exposure was 5.6 months in the core period of each study. The most commonly reported adverse reactions in patients treated with FABHALTA in APPLY-PNH (N=62) and APPOINT-PNH (N=40) were upper respiratory tract infection (19.4% and 17.5% of patients, respectively), headache (17.7% and 27.5%), diarrhea (14.5% and 7.5%), and abdominal pain (14.5% and 7.5%).

Table 1: Adverse Reactions Reported in >5% of Patients Treated with FABHALTA

	APPLY-PNH core period	
	LNP023 200 mg b.i.d. N=62 n (%)	**Anti-C5 N=35 n (%)**
Upper respiratory tract infections[1]	12 (19.4)	7 (20.0)
Headache	11 (17.7)	1 (2.9)
Diarrhoea	9 (14.5)	2 (5.7)
Abdominal pain[2]	9 (14.5)	1 (2.9)
Nausea	6 (9.7)	1 (2.9)
Arthralgia	5 (8.1)	1 (2.9)
Urinary tract infection	5 (8.1)	1 (2.9)
Dizziness	4 (6.5)	0
Platelet count decreased[3]	4 (6.5)	0
Bronchitis[4]	4 (6.5)	0

[1]Upper respiratory tract infections includes preferred terms of Nasopharyngitis, Pharyngitis, Sinusitis, Upper respiratory tract infection

[2]Abdominal pain includes preferred terms of Abdominal pain, Abdominal pain upper and Abdominal tenderness

[3]Platelet count decreased includes preferred terms of Thrombocytopenia and Platelet count decreased

[4]Bronchitis includes preferred terms Bronchitis, Bronchitis haemophilus and Bronchitis bacterial

Description of select adverse drug reactions

Platelet count decreased

Decreases in platelet counts were generally mild and transient. Some patients with concurrent anti-platelet antibodies or idiopathic bone marrow aplasia with pre-existing thrombocytopenia had further decreases to Grade 3 or 4 (based on CTCAE version 4.03).

Infections

In PNH clinical Phase 3 studies, 1 out of 102 PNH patients reported serious bacterial pneumonia while receiving treatment with FABHALTA. The patient, who was in APPOINT-PNH Phase 3 study, had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B and recovered following treatment with antibiotics while continuing treatment with FABHALTA.

Laboratory and vital signs

Blood cholesterol and blood pressure increased:

In APPLY-PNH and APPOINT-PNH, mean increases from baseline of approximately 37 mg/dL (0.952 mmol/l) and 17 mg/dL (0.433 mmol/l), respectively, were seen at month 6 for total cholesterol, and 32 mg/dL (0.830 mmol/l) and 18 mg/Dl (0.467 mmol/l), respectively for LDL-cholesterol. The mean values remained within the normal ranges. Increases in blood pressure, particularly diastolic blood pressure (DBP), were also observed (mean increase 4.4 mmHg in APPLY-PNH and 3.4 mmHg in APPOINT-PNH 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. The clinical relevance of such findings should be assessed based on individual patient characteristics and the patient should be managed accordingly.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Limited data are available with regard to overdose in humans. During clinical studies, a few patients took up to 800 mg FABHALTA daily and this was well tolerated. In healthy volunteers, the highest dose was 1200 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Complement inhibitors, ATC code: L04AJ08.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway while leaving the direct signalling from the lectin and classical pathways intact. Inhibition of FB prevents the activity of alternative pathway related C3 convertase and the subsequent formation of C5 convertase.

In PNH, intravascular haemolysis (IVH) is mediated by the downstream membrane attack complex (MAC), while extravascular haemolysis (EVH) is facilitated by opsonisation with C3 fragments. Iptacopan acts proximally in the alternative pathway of the complement cascade to control both C3-mediated EVH and terminal complement-mediated IVH.

Pharmacodynamics

The onset of inhibition of the alternative complement pathway biomarkers, *ex vivo* alternative pathway assay and plasma Bb (fragment Bb of FB), was ≤2 hours after a single iptacopan dose in healthy volunteers.

In PNH patients receiving concomitant anti-C5 treatment and iptacopan 200 mg twice daily, the *ex vivo* alternative pathway assay and plasma Bb decreased from baseline by 54.1% and 56.1%, respectively, on the first observation on Day 8. In treatment-naïve PNH patients, these same biomarkers decreased from baseline by 78.4% and 58.9%, respectively, on the first observation after 4 weeks of treatment with iptacopan 200 mg twice daily.

In PNH patients on concomitant anti-C5 treatment and iptacopan 200 mg twice daily, the mean PNH red blood cells (RBC) clone size was 54.8% at baseline and increased to 89.2% after 13 weeks; the proportion of PNH Type II + III RBCs with C3 deposition was 12.4% at baseline and decreased to 0.2% after 13 weeks. In treatment-naïve PNH patients, the mean PNH RBC clone size was 49.1% at baseline

and increased to 91.1% after 12 weeks; there were negligible PNH Type II + III RBCs with C3 deposition in this population due to the predominance of IVH.

Iptacopan reduces serum LDH levels. In PNH patients previously treated with eculizumab, all patients treated with iptacopan 200 mg twice daily achieved a reduction of LDH levels to <1.5 times upper limit of normal (ULN) after 13 weeks and maintained the effect through the end of the study. 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 the end of the study.

Cardiac electrophysiology

In a QTc clinical study in healthy volunteers, single supra-therapeutic iptacopan doses up to 1200 mg (which provided greater than 4-fold peak concentration of the MRHD) showed no effect on cardiac repolarisation or QT interval.

Clinical trials

The efficacy and safety of FABHALTA in adult patients with PNH were evaluated in two multi-centre, open-label, 24-week Phase 3 studies: an active comparator-controlled study (APPLY-PNH; NCT04558918) and a single arm study (APPOINT-PNH; NCT04820530).

APPLY-PNH: anti-C5 treatment experienced patients with PNH

APPLY-PNH enrolled adult PNH patients 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 randomization.

Ninety-seven patients were randomized in 8:5 ratio either to receive FABHALTA 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 randomized controlled period (RCP). Randomization was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months. Following completion of the 24-week RCP, all patients were eligible to enrol in a 24-week treatment extension period and receive FABHALTA monotherapy. Subsequently, patients were eligible to enter a separate long-term extension study.

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

Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 2). The mean time on prior anti-C5 treatment was 3.8 and 4.2 years for FABHALTA and anti-C5 groups, respectively. The baseline mean PNH RBC clone size (Type II + III) was 64.6% for FABHALTA and 57.4% for the anti-C5 group. Mean baseline haemoglobin was 8.9 g/dL for both groups, with approximately 57% and 60% of patients requiring a transfusion in the 6 months prior to randomization, in the FABHALTA and anti-C5 groups, respectively. The mean baseline LDH level was 269.1 U/L for FABHALTA and 272.7 U/L for the anti-C5 group. There were 19.4% and 28.6% of patients with a history of MAVEs in the FABHALTA and anti-C5 groups, respectively.

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

Table 2 Patient Baseline Demographics and Characteristics in APPLY- PNH

Parameters	Statistics	FABHALTA (n=62)	Anti-C5 (n=35)
Age (years)	Mean (SD) min, max	51.7 (16.9) 22, 84	49.8 (16.7) 20, 82
Sex			
Female	n (%)	43 (69.4)	24 (68.6)
Race			
Asian	n (%)	12 (19.4)	7 (20.0)
Black or African American	n (%)	2 (3.2)	2 (5.7)
White or Caucasian	n (%)	48 (77.4)	26 (74.3)
Ethnicity			
Hispanic or Latino	n (%)	8 (12.9)	2 (5.7)
Not Hispanic or Latino	n (%)	51 (82.3)	27 (77.1)
Not reported/unknown	n (%)	3 (4.8)	6 (17.1)
Haemoglobin level (g/dL)	Mean (SD)	8.9 (0.7)	8.9 (0.9)
LDH level (U/L)	Mean (SD)	269.1 (70.1)	272.7 (84.8)
Absolute reticulocyte count (ARC) (10^9/L)	Mean (SD)	193.2 (83.6)	190.6 (80.9)
At least one transfusion in 12 months prior to screening	n (%)	37 (59.7)	22 (62.9)
At least one transfusion in 6 months prior to randomization	n (%)	35 (56.5)	21 (60.0)
Number of transfusions in 6 months prior to randomization among patients who had a transfusion	Mean (SD)	3.1 (2.6)	4.0 (4.3)
History of MAVEs (including thrombosis)	n (%)	12 (19.4)	10 (28.6)
Disease duration (years)	Mean (SD)	11.9 (9.8)	13.5 (10.9)

Abbreviations: LDH, lactate dehydrogenase; MAVEs, major adverse vascular events; SD, standard deviation.

Efficacy was based on two primary endpoints to demonstrate superiority of FABHALTA 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. Secondary endpoints included transfusion avoidance, change from baseline in haemoglobin levels, change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, occurrence of clinical breakthrough haemolysis and change from baseline in absolute reticulocyte counts.

FABHALTA was superior to anti-C5 treatment, with a significant difference in response rate of 80.2% (82.3% vs 2%) for haemoglobin improvement (sustained increase of haemoglobin levels ≥ 2 g/dL from baseline) and 67% (68.8% vs 1.8%) for sustained haemoglobin level ≥12 g/dL without a need for RBC transfusion for both primary endpoints, after 24 weeks of treatment ($p<0.0001$) (see Table 3).

Overall, more patients achieved haemoglobin improvement in the FABHALTA group (51/60) compared to the anti-C5 group (0/35), and sustained haemoglobin ≥12 g/dL (42/60 in the FABHALTA group compared to 0/35 in the anti-C5 group) without a need for RBC transfusion (see Table 3).

FABHALTA was also superior to anti-C5 treatment for transfusion avoidance rate with a treatment difference of 68.9% (94.8% vs 25.9% (p<0.0001)) and change from baseline in haemoglobin level (treatment difference of +3.66 g/dL; p<0.0001). The treatment effect of FABHALTA on haemoglobin was seen as early as Day 7 and sustained during the study (see Figure 1).

FABHALTA was superior to anti-C5 treatment in improving fatigue as assessed by FACIT-Fatigue (treatment difference of +8.29 points; p < 0.001), and patients treated with FABHALTA experienced clinically meaningful improvements in patient reported fatigue from baseline (+8.59 points).FABHALTA was also superior to anti-C5 treatment in annualized rate of clinical breakthrough haemolysis (treatment difference of 90%; p=0.01) and reduction in absolute reticulocyte count from baseline (treatment difference of -116.2x10^9/L; p<0.0001) consistent with the inhibition of EVH.

The LDH ratio to baseline was similar for both treatment groups, demonstrating that FABHALTA maintained control of IVH following discontinuation of anti-C5 treatment (see Table 3).

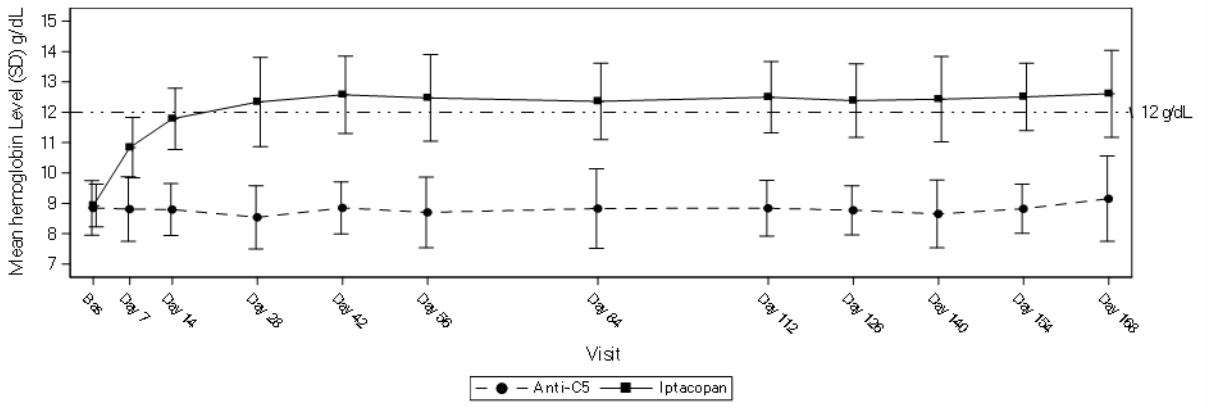
Table 3 Efficacy results for the 24-week randomized treatment period in APPLY-PNH

Endpoints	**FABHALTA (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) Response rate[c] (%)	51/60[b] 82.3	0/35[b] 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 Response rate[c] (%)	42/60[b] 68.8	0/35[b] 1.8	 67.0 (56.4, 76.9) <0.0001
Secondary endpoints			
Number of patients avoiding transfusion[d,e] Transfusion avoidance rate[c] (%)	59/62[b] 94.8	14/35[b] 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

Endpoints	FABHALTA (N=62)	Anti-C5 (N=35)	Difference (95% CI) p-value
Clinical breakthrough haemolysis [h,i], % (n/N)	3.2 (2/62)	17.1 (6/35)	
Annualized rate of clinical breakthrough haemolysis	0.07	0.67	RR=0.10 (0.02, 0.61) 0.01
Absolute reticulocyte counts 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	
Annualized rate of MAVEs[h]	0.03	0	0.03 (-0.03, 0.10) 0.32

Abbreviations: RR, rate ratio; LDH, lactate dehydrogenase; MAVEs, major adverse vascular events.
[a] Assessed between Day 126 and 168.
[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 adjusted proportion.
[d] Assessed between Day 14 and 168.
[e] Transfusion avoidance is defined as absence of administration of packed-red blood cell transfusions or meeting the criteria for transfusion between Day 14 and 168.
[f] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were excluded from the analysis.
[g] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were included in the analysis.
[h] Assessed between Day 1 and 168.
[i] Clinical breakthrough haemolysis 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-times ULN and increased as compared to the last 2 assessments).

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



**Note: The figure includes all haemoglobin data collected in the study, irrespective of transfusion.*

The results for the primary endpoints were consistent across the predefined subgroups studied, including disease duration, age, sex, baseline haemoglobin, history of MAVEs, previous anti-C5 treatment (eculizumab or ravulizumab), the need for transfusion in the last 6 months, number of transfusions in the last 6 months (<2 or ≥2), LDH level at baseline, and duration of previous anti-C5 treatment.

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 ULN, who were not previously treated with a complement inhibitor. All 40 patients received FABHALTA 200 mg orally twice daily during the 24-week open-label core treatment period. Subsequently, patients were eligible to enrol in a 24-week treatment extension period and continue to receive FABHALTA, followed by a separate long-term extension study.

Patients were required to be vaccinated against *Neisseria meningitidis* and recommended to be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* Type B. If the patient had not been previously vaccinated or if a booster was required, vaccination was administered at least 2 weeks prior to or up to 2 weeks after the first dose. If FABHALTA treatment was initiated earlier than 2 weeks after vaccination, antibacterial drug prophylaxis treatment was administered.

Table 4 shows the patient baseline demographics and disease characteristics. No patients discontinued from the core treatment period of the study.

Table 4 Patient baseline demographics and characteristics in APPOINT-PNH

Parameters	**Statistics**	**FABHALTA (n=40)**
Age (years)	Mean (SD) min, max	42.1 (15.9) 18, 81
Sex Female	 n (%)	 17 (42.5)
Haemoglobin level (g/dL)	Mean (SD)	8.2 (1.1)
LDH level (U/L)	Mean (SD)	1,698.8 (683.3)
Absolute reticulocyte count (ARC) (10^9/L)	Mean (SD)	154.3 (63.7)
At least one transfusion in the last 12 months prior to screening	n (%)	27 (67.5)
At least one transfusion in the last 6 months prior to treatment	n (%)	28 (70.0)
Number of transfusions in last 6 months prior to treatment among patients who had a transfusion	Mean (SD)	3.1 (2.1)
History of MAVEs (including thrombosis)	n (%)	5 (12.5)
Disease duration (years)	Mean (SD)	4.7 (5.5)

Efficacy was based on the primary endpoint assessing the effect of FABHALTA 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). Secondary endpoints included: sustained haemoglobin ≥12 g/dL (without a need for RBC transfusion) after 24 weeks, transfusion avoidance, change from baseline in haemoglobin levels, change from baseline in FACIT-Fatigue scores, occurrence of clinical breakthrough haemolysis and change from baseline in absolute reticulocyte counts.

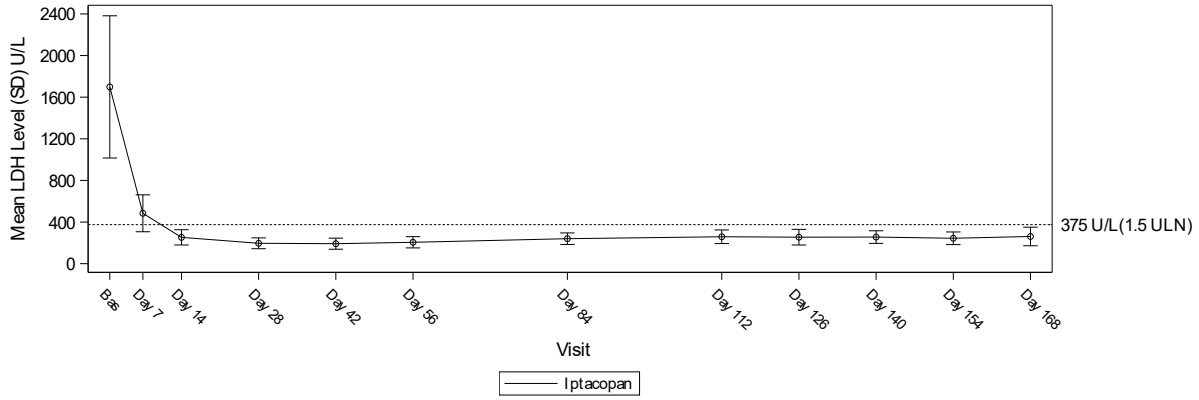
FABHALTA treatment resulted in a response rate of 92.2% (95% CI: 82.5, 100.0) for haemoglobin improvement, without a need for RBC transfusion, after 24 weeks. The response rate for patients achieving haemoglobin ≥12 g/ dL, without a need for RBC transfusion was 62.8% (95% CI: 47.5, 77.5). FABHALTA treatment led to transfusion avoidance rate of 97.6% (95% CI: 92.5, 100.0). Patients treated with FABHALTA experienced clinically meaningful improvements in patient reported fatigue (FACIT-Fatigue score change from baseline +10.8; 95% CI: 8.7, 12.8). No patients experienced clinical breakthrough haemolysis or MAVEs. When compared to baseline, in patients treated with FABHALTA, haemoglobin levels increased by 4.3 g/dL (95% CI: 3.9, 4.7), absolute reticulocyte counts changed by -82.5 x 10^9/L (95% CI: -89.3, -75.6), and the LDH percent change was -83.6% (95% CI: -84.9, -82.1) after 24 weeks. The treatment effect of FABHALTA on LDH was seen as early as Day 7 and reached <1.5 ULN by Day 14, which was sustained during the study. (See Table 5 and Figure 2).

Table 5 Efficacy results for the 24-week core treatment period in APPOINT-PNH

Endpoints	**FABHALTA (N=40) 95% CI**
Primary endpoint	
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin levels ≥ 2 g/dL from baseline in the absence of transfusions) Response rate[c] (%)	31/33[b] 92.2 (82.5, 100.0)[d]
Secondary endpoints	
Number of patients achieving sustained haemoglobin level ≥12g/dL[a] in the absence of transfusions Response rate[c] (%)	19/33[b] 62.8 (47.5, 77.5)
Number of patients avoiding transfusion[e,f] Transfusion avoidance rate[c] (%)	40/40[b] 97.6 (92.5, 100.0)
Haemoglobin level change from baseline (g/dL) (adjusted mean[a])	+4.3 (3.9, 4.7)
FACIT-Fatigue score change from baseline (adjusted mean[a])	+10.8 (8.7, 12.8)
Clinical breakthrough haemolysis[g,h], % (n/N) Annualized rate of clinical breakthrough haemolysis	0/40 0.0 (0.0,0.2)
Absolute reticulocyte counts change from baseline (10^9/L) (adjusted mean[a])	-82.5 (-89.3, -75.6)
LDH percent change from baseline (adjusted mean[a])	-83.6 (-84.9, -82.1)
Percent of patients with MAVEs[h]	0.0
[a] Assessed between Day 126 and 168.	

Endpoints	FABHALTA (N=40) 95% CI
[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 adjusted proportion. [d] The threshold for demonstration of benefit was 15%, representing the rate that would have been expected on anti-C5 treatment. [e] Assessed between Day 14 and 168. [f] Transfusion avoidance is defined as absence of administration of packed-red blood cell transfusions between Day 14 and Day 168 or meeting the criteria for transfusion between Day 14 and 168. [g] 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-times ULN and increased as compared to the last 2 assessments). [h] Assessed between Day 1 and 168. [i] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were excluded from the analysis. [j] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were included in the analysis.	

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



The results for the primary endpoint were consistent across the predefined subgroups examined, including disease duration, age, sex, baseline haemoglobin, history of MAVEs, need for transfusion in the last 6 months, and number of transfusions in the last 6 months (<2 or ≥2).

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). The C_{max} and AUC data from a food-effect study involving administration of iptacopan to healthy volunteers under fasting conditions or with a high-fat meal indicated that exposure to iptacopan is not affected by food. Therefore, FABHALTA 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 relevant clinical plasma

concentrations. After administration of iptacopan 200 mg twice daily, the apparent volume of distribution at steady state was approximately 288 L.

Metabolism

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 (98%) with a small contribution from CYP2D6 (2%). Glucuronidation (UGT1A1, UGT1A3, UGT1A8) is a minor pathway. In plasma, iptacopan was the major component accounting for 83% of the $AUC_{0\text{-}48hr}$. Two acyl glucuronides were the only metabolites detected in plasma and were minor, accounting for 8% and 5% of the $AUC_{0\text{-}48hr}$. Iptacopan metabolites are not considered pharmacologically active.

Excretion

In a human study, 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 giving total mean excretion of >96% of the dose. Specifically, 17.9% of the dose was excreted as parent iptacopan into the urine and 16.8% in faeces. The half-life ($t_{1/2}$) of iptacopan at steady state is approximately 25 hours after administration of FABHALTA 200 mg twice daily.

Linearity/non-linearity

At doses between of 25 mg and 200 mg twice daily, iptacopan was overall under dose proportional. However, oral doses of 100 mg and 200 mg were approximately dose proportional.

Special populations

A population pharmacokinetic (PK) analysis was conducted on data from 234 patients. Age, 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.

Use in hepatic impairment

Based on a study in patients with mild, moderate, or severe hepatic impairment, a negligible effect on the exposure of iptacopan was observed. An approximately 1.04-fold increase in iptacopan C_{max} was observed in patients with mild hepatic impairment (n=8) and no changes were observed in patients with moderate (n=8) or severe (n=6) hepatic impairment. Increase in AUCinf in patients with mild and severe hepatic impairment was 1.03-fold while there was no change for patients with moderate hepatic impairment.

No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment (see section 4.2 Dose and method of administration).

Use in renal impairment

Only 17.9% of iptacopan was excreted in the urine as parent drug. Kidney is therefore a minor route of elimination. The effect of renal impairment on the clearance of iptacopan was assessed using a population pharmacokinetic analysis. There were no clinically relevant differences in the clearance of iptacopan between patients with normal renal function and patients with mild (eGFR 60- <90 mL/min/1.73m2) or moderate (eGFR 30- <60 mL/min/1.73m2) renal impairment, and no dose adjustment is required (see section 4.2 Dose and method of administration). Patients with severe renal impairment or on dialysis have not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Iptacopan showed no genotoxicity in assays for bacterial reverse mutation (Ames test), chromosomal aberrations *in vitro* (in human lymphocytes) or in the *in vivo* rat peripheral blood micronucleus test.

Carcinogenicity

The carcinogenic potential of iptacopan was investigated in a 6-month study in transgenic (Tg.rasH2) mice and in a 2-year study in rats, both conducted by the oral route. Iptacopan was not carcinogenic in either species up to the highest doses tested (1000 mg/kg/day in mice and 750 mg/kg/day in rats). These doses yield exposure to iptacopan 4.4-times higher in mice (based on plasma AUC for total drug) and 44-times higher in rats (based on unbound AUC) than in patients at the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule fill: None

Capsule shell: Hard gelatin, red iron oxide (E 172), titanium dioxide (E 171), and yellow iron oxide (E 172).

Printing ink: Black iron oxide (E 172), concentrated ammonia solution (E 527), propylene glycol (E 1520), potassium hydroxide (E 525), and shellac (E 904).

6.2 INCOMPATIBILITIES

FABHALTA is not anticipated to have clinically relevant interactions with other drug products (see Section 4.5 – Interactions with other medicines and other forms of interactions).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

FABHALTA must be kept out of the reach and sight of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Pack of 56 hard capsules in PVC/PE/PVdC (triplex) blister packs backed with aluminium foil.

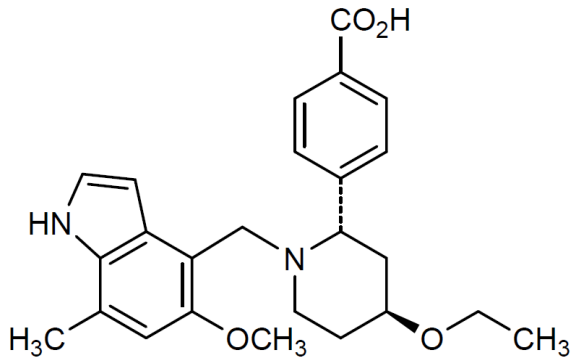
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Iptacopan hydrochloride monohydrate has a molecular formula $C_{25}H_{30}N_2O_4.HCl.H_2O$ and a molecular mass of 477.00. It is a powder with pKa values of 8.9 and 3.7 and pH-dependant solubility.

Chemical structure



CAS number

1644670-37-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription medicine

8 SPONSOR

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