swissmedic

Date: 30 December 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Fabhalta

International non-proprietary name: iptacopan
Pharmaceutical form: capsule
Dosage strength(s): 200 mg
Route(s) of administration: oral
Marketing authorisation holder: Novartis Pharma Schweiz AG
Marketing authorisation no.: 68603
Decision and decision date: approved on 29 August 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
b.i.d.	bis in die, twice a day
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
E_{max}	Maximum drug effect
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GPI	Glycophosphatidylinositol
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
T_{max}	Time to peak drug concentration
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for iptacopan in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 of the TPA. Orphan drug status was granted on 2 November 2021.

2.2 Indication and dosage

2.2.1 Requested indication

Fabhalta is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

2.2.2 Approved indication

Fabhalta is indicated as monotherapy for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have had an inadequate response despite at least 6 months of treatment with a C5 inhibitor (see "Clinical efficacy").

2.2.3 Requested dosage

The proposed dose of iptacopan is 200 mg b.i.d., as a capsule to be taken orally with or without food. If a dose is missed, the patient should be advised to take iptacopan as soon as possible (even if it is soon before the next scheduled dose) and then to resume the regular dosing schedule.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	20 June 2023
Formal control completed	28 June 2023
List of Questions (LoQ)	6 October 2023
Response to LoQ	20 December 2023
Preliminary decision	19 March 2024
Response to preliminary decision	15 May 2024
Labelling corrections	12 July 2024
Response to labelling corrections	24 July 2024
Final decision	29 August 2024
Decision	approval

3 Medical context

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disease with an incidence of 1-1.5/ 1 million. PNH is characterised by acquired (somatic) mutations of the PIG-A gene in pluripotent haematologic stem cells and other, not fully understood, mechanisms. Ultimately, this results in glycophosphatidylinositol (GPI)-deficient peripheral blood cells. The GPI anchor is essential for linking certain membrane proteins in eukaryotic cells. In PNH pathogenesis, the resulting deficiency of complement-regulating proteins (in particular CD55 and CD59) on erythrocytes is of particular relevance. This deficiency leads to complement-mediated lysis of erythrocytes. Lysis can occur intravascularly and extravascularly. Erythrolysis results in accelerated NO-consumption, reduced NO-replenishment, and consequently endothelial and thrombocyte activation, which may lead to thrombotic incidents. Excessive haemoglobin filtration results in renal deficiency, and haemolytic anaemia leads to symptoms of anaemia and high erythrocyte turnover with associated nutrient consumption.

The clinical presentation varies considerably. Frequent clinical signs and symptoms at primary diagnosis include fatigue and impaired quality of life (96%), anaemia (88%), dyspnoea (66%), chronic kidney disease (64%), abdominal pain (57%), pulmonary hypertension (47%), erectile dysfunction (47%), dysphagia (41%), and thrombosis (40%). Haemoglobinuria, on the other hand, occurs more rarely (26%). PNH is a serious and potentially life-threatening disease. Historical retrospective data from a UK cohort demonstrate a reduced life expectancy of PNH patients.

The central role of the complement system in PNH has led to the successful use of complement inhibitors in the treatment of PNH. The incorporation of the first C5 inhibitors in routine PNH treatment improved the PNH substantially. Retrospective analyses demonstrated near-normal life expectancy of PNH patients using C5 Inhibitors.

As a consequence, C5 inhibitors are the standard first-line treatment for symptomatic PNH patients. They mainly inhibit intravascular lysis. A relevant share of patients experiences insufficient Hb increases, or Hb drops under treatment with C5 inhibitors. Primary reasons are bone marrow disorders and C3-mediated extravascular haemolysis. Inadequate Hb-increases are attributable to C3-mediated extravascular haemolysis in approximately 25-50% of cases. Components of the complement cascade upstream of C5 are not affected by C5 inhibition. If C3/C3-fragments bind to erythrocytes, this leads to extravascular lysis (mediated by macrophages), mainly in the liver, and to a lesser extent in the spleen. Clinically significant extravascular haemolysis is characterised by relevant laboratory findings such as a fall in Hb and an increase in LDH, as well as clinical signs and symptoms.

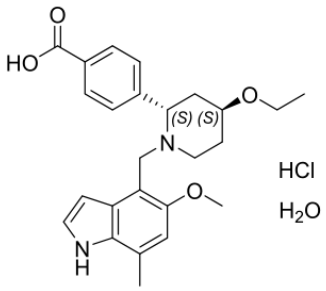
Extravascular haemolysis is treatable with complement modulators targeting components upstream of C5, with C3 inhibitors also approved in Switzerland for PNH patients with insufficient response to C5 inhibitors.

4 Quality aspects

4.1 Drug substance

INN:	Iptacopan
Chemical name:	(2S,4S)-2-(4-Carboxyphenyl)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-1-ium chloride—water (1/1)
Molecular formula:	Active moiety: $C_{25}H_{30}N_2O_4$
	Salt and solvate (hydrate) form: $C_{25}H_{30}N_2O_4.HCl.H_2O$
Molecular mass:	Active moiety: 422.52 g/mol
	Salt and solvate (hydrate) form: 477.00 g/mol

Molecular structure:



Physicochemical properties: Iptacopan is a white or almost white to pale purplish-pink powder. Itis slightly soluble in water and very slightly to sparingly soluble in aqueous buffers. The drug substance has two stereogenic centres. Their absolute configurations are 2S and 4S. The molecule is used as single enantiomer. Iptacopan hydrochloride monohydrate is slightly hygroscopic.

Synthesis: The drug substance is manufactured by a multiple step chemical synthesis with final isolation by crystallisation.

Specification: The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, particle size, assay, impurities, and microbiological quality.

Stability: Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug product

Description and composition: Iptacopan 200 mg hard capsules are an immediate-release dosage form for oral administration. The hard capsules have a pale yellow opaque cap and body with black imprint “LNP200” on the body and “NVR” on the cap, containing white or almost white to pale purplish-pink powder.

Pharmaceutical development: Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA), and the Critical Process Parameters (CPP).

Manufacture: The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included. Adequate validation data pertaining to the commercial manufacturing process are available.

Specification: The drug product specification covers relevant physicochemical characteristics and identification, assay, and purity tests are included as well. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.

Container closure system: The drug product is packaged into blisters consisting of PVC/PE/PVdC-aluminium.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Iptacopan inhibited human complement factor B (FB) binding with an IC_{50} of 9.6 nM. Binding to human complement factor D was not affected at concentrations up to 100 µM. In addition, iptacopan did not inhibit binding to any of the other proteases tested at concentrations up to 100 µM. Iptacopan inhibited alternative pathway (AP) complement activation in mouse, rat, rabbit, pig, dog, monkey, and human serum with IC_{50} and IC_{90} values in the range of 100-600 nM and 300-1600 nM, respectively (in the presence of 50% serum). Unlike eculizumab, iptacopan did not inhibit the classical pathway at concentrations up to 100 µM in human serum. In a surrogate assay with PHN-like human erythrocytes, iptacopan suppressed haemolysis with an IC_{50} of 104 nM and an IC_{90} of 339 nM (in the presence of 50% serum). Iptacopan also blocked coating of erythrocytes with C3d fragments. In contrast, eculizumab inhibited haemolysis (IC_{50} and IC_{90} values of 132 and 264 nM, respectively) but had very little impact on C3 coating. Furthermore, iptacopan inhibited haemolysis of sheep red blood cells incubated with serum derived from patients with AP-mediated nephritides at 150 and 600 nM.

Iptacopan showed dose-dependent inhibition of lipopolysaccharide-induced complement activation in mice. Complete inhibition of C3d and iC3b in plasma and tissue was achieved after a single dose of 30 mg/kg. In a nephritis rat model dependent on complement activation, iptacopan at 20 and/or 60 mg/kg b.i.d. prevented development and progression of proteinuria, glomerulopathy, and tubular degeneration. Inhibition of complement activation was demonstrated by the absence of glomerular C3 deposition.

In conclusion, the pharmacology of iptacopan as an inhibitor of FB and, consequently, the AP for treatment of PNH has been sufficiently characterised from a nonclinical perspective.

Iptacopan did not show any activity in secondary pharmacology screens, with the exception of the ATP-binding mTOR kinase (IC_{50} of 9.9 µM). The relevance of this observation is unknown.

Iptacopan did not suppress T-cell dependent B-cell (antibody) response in mice, rats, or dogs.

The increased risk of infections with encapsulated bacteria (i.e. *Neisseria meningitidis* and *Streptococcus pneumoniae*) and its management by vaccination is adequately addressed in the Information for healthcare professionals.

The safety pharmacology studies in rats did not reveal any effects of iptacopan on the central nervous or respiratory system at plasma concentrations approximately 10-fold human C_{max} at therapeutic dose.

Iptacopan showed no effects on the major cardiac ion channels *in vitro*. In rats, iptacopan had no effect on blood pressure or heart rate at exposures approximately 10-fold human C_{max} at therapeutic dose. In monkeys, a single oral dose of iptacopan led to a dose-dependent QTc prolongation at exposures ≥21-fold human C_{max} at therapeutic dose. No QTc prolongation was noted in dogs or in the Phase 1 studies in healthy volunteers at doses up to 1200 mg (resulting in C_{max} approximately 4-fold human C_{max} at therapeutic dose).

In dogs, there was a decrease in blood pressure associated with an increase in heart rate at exposures ≥8-fold human C_{max} at therapeutic dose. A decrease in total peripheral resistance was also recorded. The increase in heart rate was also observed in the repeat-dose toxicity studies. The effect appeared to attenuate over time in the 39-week study. Persistent tachycardia associated with focal cell degeneration and fibrosis (mainly papillary muscle) was only observed at ≥300 mg/kg/day in the 2- and 4-week studies. These findings were considered likely to be related to ischaemia associated with the increased heart rate as the papillary muscle in the dog heart is known to be sensitive to this type of effect. There was no increase in blood pressure or heart rate in rats and no increase in heart

rate in monkeys, suggesting that dogs are the most sensitive species for the haemodynamic effects of iptacopan. There were no changes in heart rate or blood pressure in the Phase 1 studies in healthy volunteers at doses up to 1200 mg (resulting in C_{max} approximately 4-fold human C_{max} at the therapeutic dose).

5.2 Pharmacokinetics

Bioavailability after oral administration was approximately 40% to 70% in mice, rats, and dogs. T_{max} after oral dosing was 0.25 to 2 h. The elimination half-life of iptacopan after IV dosing was 2.9 to 7.5 h. After repeated oral doses to rats or dogs, both C_{max} and AUC increased with dose in an approximately proportional manner. No accumulation was noted after repeated dosing. There were no sex-related differences in exposure.

Plasma protein binding and blood to plasma concentration ratios were concentration-dependent in mice, rats, dogs, and humans. The observed saturable binding of iptacopan in plasma may be explained by binding of iptacopan to its target i.e. FB, which is highly abundant in plasma. Iptacopan-derived radioactivity distributed into tissues, with the exception of the brain, and was eliminated within 24 h from most tissues. There was also a reversible affinity for melanin.

Metabolic pathways include N-dealkylation, O-deethylation, C-oxidation, and glucuronidation at the carboxyl moiety of iptacopan. The main metabolising enzymes include CYP2C8 as well as UGT1A1 and UGT1A8. In rats and humans, the major plasma component was unchanged iptacopan. The metabolite M8, the glucuronide of iptacopan, contributes to more than 10% of the AUC in human plasma and is adequately qualified in the toxicity studies in rats and dogs.

In rats and humans, iptacopan is mainly eliminated via metabolism followed by biliary/faecal excretion. Some unchanged iptacopan was excreted into urine, with humans showing higher renal excretion, and bile.

5.3 Toxicology

The applicant conducted a full toxicology programme in line with ICH M3(R2). The repeat-dose toxicity studies were conducted in rats and dogs, both of which are pharmacologically relevant animal species. The main human metabolite (M8) in plasma was also present in rat and dog plasma. Iptacopan was administered orally, in line with the intended clinical route of administration. The duration of the repeat-dose toxicity studies was appropriate for a product intended for long-term use.

Single oral doses of iptacopan up to 1000 mg/kg to dogs or up to 600 mg/kg to monkeys were well tolerated. The main target organs in the repeat-dose toxicity studies were the thyroid, testis, and possibly the bone marrow. The cardiac findings are discussed in the safety pharmacology section. Severe bone marrow toxicity occurred in a single dog at an exposure 14-fold human AUC at therapeutic dose (or 49-fold based on unbound iptacopan). There were no adverse effects on red blood cells or haemoglobin in clinical studies. The follicular cell hypertrophy in the thyroid was not considered adverse in the 26-week rat or 39-week dog studies. There were no changes in thyroid hormones during the clinical programme. The tubular degeneration in the testis was only consistently observed in dogs at an exposure 3.6-fold human AUC at therapeutic dose (or 17-fold based on unbound iptacopan). The finding was of minimal to mild severity, did not progress in severity with longer treatment duration, and was reversible in both rats and dogs. There were no significant effects on sperm parameters or morphology. There were no effects in the rat male fertility study (see below). In addition, no obvious fertility issues were observed in the FB knockout mouse or patients with genetic mutations in the AP. There were no changes in reproductive hormones during the clinical programme. At the NOAEL in the 26-week rat study, exposure was 6.5-fold human AUC at therapeutic dose or 22-fold based on unbound iptacopan. In the 39-week dog study, exposure at the NOAEL was 0.8-fold human AUC at therapeutic dose or 1.8-fold based on unbound iptacopan for

males and 3.0-fold human AUC at therapeutic dose or 9.5-fold based on unbound iptacopan for females. These safety margins can be accepted for a product intended for the treatment of PNH, provided the safety profile in patients is reassuring.

Iptacopan was not genotoxic. Carcinogenicity studies in transgenic rasH2 mice and in rats showed no carcinogenic potential for iptacopan.

Iptacopan did not impair male fertility in rats at exposures approximately 5.7-fold human AUC at therapeutic dose or 20-fold based on unbound iptacopan. The fertility and early embryonic development study in female rats revealed an increase in pre- and postimplantation losses at exposures approximately 2.4-fold human AUC at therapeutic dose or 6.9-fold based on unbound iptacopan. No embryofetal toxicity or teratogenicity was noted in rats (at exposures 5.4-fold human AUC at therapeutic dose or 18-fold based on unbound iptacopan) or in rabbits (at exposures 7.8-fold human AUC at therapeutic dose). The pre- and postnatal development study in rats did not identify any toxicity to the F0 generation or effects on development of the F1 generation at exposures approximately 5.4-fold human AUC at therapeutic dose or 18-fold based on unbound iptacopan. Due to the risks to the mother and fetus associated with untreated PNH in pregnancy, the applicant proposes that treatment with iptacopan may be considered in women who are pregnant or intend to become pregnant after a risk-benefit assessment. This can be accepted from a nonclinical perspective if supported by the clinical assessor. The toxicity study in juvenile dogs, where animals were dosed for 52 weeks starting from PND 28, did not reveal any additional target organ but showed cardiac findings that were more pronounced than in adult animals. The NOAEL was 5 mg/kg/day (exposure 0.9-fold human AUC at therapeutic dose or 2.4-fold based on unbound iptacopan).

Iptacopan showed weak phototoxicity potential *in vitro* that could not be confirmed *in vivo*.

There were no issues with impurities.

The applicant provided a satisfactory ERA. All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. The toxicity study in juvenile dogs requested in the PIP was completed and the report is included in the MAA.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered adequate to support the approval of iptacopan in the proposed indication. All safety-relevant nonclinical data are included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

Biopharmaceutical development
Throughout the entire clinical programme, 2 slightly different formulations of iptacopan were developed and used. Whereas the early-phase clinical formulation contained the neat drug substance as an anhydrous hydrochloride salt in hard gelatine capsules, iptacopan was processed as a monohydrate of the hydrochloride salt in the late-phase clinical formulation. The final to-be-marketed drug product is supplied as a 200 mg strength immediate-release hard gelatine capsule. The commercial formulation is identical to the late-phase clinical formulation used in the Phase 3 studies with minor changes in capsule colour and imprint.

Following a single dose administration of 100 mg iptacopan, a high-fat breakfast did not have an impact on iptacopan exposure. The approved dosing recommendation to take the tablet irrespective of food consumption was applied in the Phase 3 studies.

ADME
The PK and PD profiles of in healthy subjects following single (5 mg to 1200 mg) and multiple doses (25 mg to 200 mg b.i.d.) were evaluated in 6 Phase 1 studies. PK and PD samples were collected in 4 Phase 2 and 2 Phase 3 studies and were used for population PK as well as PK/PD analyses.

Absorption
Following a single dose of iptacopan in healthy subjects, peak plasma concentrations were reached after a median T_{max} of 1 h to 2.5 h. The absolute bioavailability of iptacopan was not determined. In view of the high solubility, the bioavailability is expected to be high. Based on the urinary and faecal excretion attributed to metabolites, the mean oral absorption of iptacopan is at least 70.6% of the administered dose.
After multiple doses of iptacopan in healthy subjects, the median T_{max} was 1 h to 2 h. Based on trough levels, steady-state plasma concentrations of iptacopan were reached after approximately 5 to 7 days. After the administration of multiple b.i.d. doses, limited accumulation with accumulation ratios <2 was observed. Overall, the intra- and inter-subject variability of iptacopan was low to moderate.

Following single and multiple doses of iptacopan, exposure increased with the dose. Overall, less than dose-proportional increases were observed across the entire dose range. However, it seems that dose proportionality was approached at steady state between the 100 mg and 200 mg doses, which would be in line with the target-mediated drug disposition of iptacopan.

Based on non-compartmental PK analysis, no significant differences were observed between healthy subjects and PNH patients.

Distribution
It was shown *in vitro* that protein binding of iptacopan decreased in a concentration-dependant manner, whereas blood-to-plasma (Cb/Cp) concentration ratios increased. This is most likely a consequence of the high-affinity binding of iptacopan to the target, i.e. factor B.
The volume of distribution of iptacopan increased with the dose. Following the b.i.d. administration of 200 mg iptacopan, the volume of distribution was determined at 288 L.

Metabolism and elimination
Iptacopan is mainly metabolised by oxidation dependent on CYP2C8 (fm = 98%), with a minor contribution from CYP2D6 and CYP1A1 accounting for approximately 50% of the administered dose. Direct acyl glucuronidation by UGT1A1 and UGT1A3 is a minor pathway. Iptacopan was excreted via faeces and urine, accounting for 71.5% and 24.8% of the total radioactivity, respectively. The predominant circulating entity was iptacopan (83%) followed by the metabolites M8 (8.05%) and M9 (5.17%). The major metabolites in faeces were M2 and M7, accounting for 27.0% and 8.32%,

respectively, of the administered radioactive dose, whereas the parent drug represented 16.8%. 17.9% of the administered radioactive dose in urine was the parent drug, and the major metabolites in urine were M1 and M9, accounting for 3.82% and 1.60%, respectively.

Clearance of iptacopan increased with the dose. Following the b.i.d. administration of 200 mg iptacopan, the half-life was determined at 25 h.

Special populations / intrinsic factors
The impact of liver function on the pharmacokinetics of iptacopan following a single dose of 200 mg iptacopan was investigated in a dedicated study in subjects with normal hepatic function and mild to severe hepatic impairment. Whereas iptacopan exposures after a single oral dose of 200 mg in subjects with mild, moderate, or severe hepatic impairment were comparable to those in matched healthy subjects, unbound exposures increased significantly up to 3.7-fold. Use in patients with severe hepatic impairment is not recommended.

27% of the subjects included in the population PK analysis had mild renal impairment, while 24% had moderate and 3% had severe renal impairment. eGFR (27.45 to 142.76 mL/min/1.73m^2) was identified as a significant covariate and was included in the final model. The apparent clearance increased with baseline eGFR, which resulted in 38% higher AUCs in patients with eGFR of 34.3 mL/min/1.73m^2. Overall, no dose adjustments are required in patients with mild and moderate renal impairment. Use in patients with severe renal impairment with or without haemodialysis is not recommended.

The PK and PD profiles of iptacopan in healthy Japanese subjects were comparable to those in White subjects.

Using data from 4 Phase 2 and s Phase 3 studies in C3G, IgAN, and PNH patients, a population PK analysis was conducted to identify factors that account for variability of the iptacopan PK. The PK of iptacopan was described by a 1-compartment model with first-order absorption (Ka), lag time to absorption (Tlag), and first-order elimination. The final model included the following covariates: body weight, baseline eGFR, and ethnicity covariates on CL/F. Iptacopan exposures decreased with increasing body weight and eGFR, whereas higher exposures were predicted in Chinese, Japanese, and other Asian patients. These differences were deemed not clinically relevant. Overall, no dose adjustments are recommended based on any of the investigated covariates including body weight, gender, age, ethnicity, and renal function (mild/moderate).

Interactions
An *in vitro* DDI risk assessment was conducted for the relevant enzymes and transporters at adequate concentrations of iptacopan. *In vitro*, iptacopan did not reversibly inhibit any of the investigated CYPs including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. No time-dependent inhibition for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 was observed: The Ki could only be determined for CYP2C8 (KI,u: 179 µM, kinact: 0.0702 min^{-1}). No *in vitro* induction of CYP1A2, CYP2B6, or CYP2C9 was observed. A weak induction of CYP3A4 of less than 20% of positive control at the highest concentration (100 µM) was detected. No inhibition of UGT1A1 was observed *in vitro*. Iptacopan was shown to be a substrate of P-gp, BCRP, MRP2, and the hepatic uptake transporters OATP1B1/3. Renal transporters were not investigated, which is acceptable considering that iptacopan CLr is lower than the average human GFR, suggesting that renal transporters do not contribute substantially to CLr. *In vitro*, iptacopan inhibited P-gp (Ki = 27.7 µM), OATPB1 (Ki = 24.9 µM), OATPB3 (Ki > 393 µM), OAT3 (Ki = 183.3 µM), OCT1 (Ki = 396.6 µM), and MATE1 (Ki =327.1 µM). No inhibition of BSEP, MRP2, BCRP, OCT2, OAT1, or MATE2-K was observed.
Based on the *in vitro* results, a clinical DDI study was conducted investigating the effect of clopidogrel (CYP2C8 inhibitor) and cyclosporine (OATP1B1/3 inhibitor) on iptacopan PK, as well as the impact of iptacopan on the PK of digoxin (P-gp substrate) and rosuvastatin (OATP substrate). Iptacopan was

shown to be a substrate of P-gp, BCRP, and MRP2 *in vitro*. However, no saturation of the efflux transporters was observed up to concentrations of 800 µM for P-gp and BCRP and 400 µM for MRP2. Considering the iptacopan C_{gut} concentrations, which were estimated at 568 µM for a 200 mg dose, no DDI study with P-gp, BCRP, or MRP2 inhibitors was conducted.
Co-administration with clopidogrel, a moderate CYP2C8 inhibitor, led to an increase of iptacopan AUC by 36%, whereas the impact on C_{max} was small. Co-administration of iptacopan with strong inhibitors of CYP2C8 is not recommended. When co-administered with cyclosporine, an inhibitor of OATP1B1/3, iptacopan C_{max} and AUC increased by 41% and 50%. Co-administration of strong inducers of CYP2C8, UGT1A1, P-gp, BCRP, and OATP1B1/3 may lead to loss of or reduced efficacy. No impact of iptacopan on the plasma PK of the P-gp and OATP substrates digoxin and rosuvastatin was observed. Caution should be exercised when iptacopan is co-administered with sensitive CYP3A4 and CYP2C8 substrates.

Mechanism of action and primary pharmacology
Iptacopan is an inhibitor of Factor B (FB), which is a central protease of the alternative complement pathway.

Exploratory biomarkers to investigate the PD of iptacopan in the Phase 1 studies included alternative complement pathway activity (Wieslab assay), classical complement pathway activity (CH50 assay), and soluble biomarkers (Bb, C5b-9). Overall, rapid, significant (>80%), and dose-dependent suppression of AP activity was observed for all (single and multiple) doses tested except for the 5 mg dose. While reduction of fragment Bb of factor B level without apparent dose dependency was observed following iptacopan administration, there was no consistent effect on the classical complement pathway activity.

Secondary pharmacology (safety)
A thorough QT/QTc study in healthy subjects suggested the absence of an unacceptable prolongation in cardiac repolarisation compared to placebo following the administration of a single supratherapeutic dose of 1200 mg iptacopan. Overall, exposures increased less than dose-proportionally. Based on C_{max}, the 1200 mg dose resulted in over 4-fold higher concentrations than obtained from the proposed 200 mg dose b.i.d. at steady state.
A concentration-QTc analysis using pooled concentration and QT data covering a dose range from 5 mg to 1200 mg did not indicate any relevant impact on the QT interval.

Exposure efficacy/safety relationship
Using data from 1 Phase 1 study in healthy subjects and 4 Phase 2 studies in C3G, IgAN, and PNH patients, the relationship between exposure and response for the alternative pathway biomarkers, serum Wieslab assay, plasma Bb, and plasma sC5b-9 were investigated.
Sigmoid E_{max} direct response models described the relationships between iptacopan and complement pathway biomarkers best. While the median exposures following the 50 mg, 100 mg, and 200 mg b.i.d. doses were above the EC90 values for Bb and plasma sC5b9, this is only the case for the 200 mg dose with regard to the Wieslab assay. Covariates other than population type or baseline biomarker levels did not significantly impact the exposure-response relationships.

6.2 Dose finding and dose recommendation

Iptacopan 200 mg twice daily (b.i.d.) dosing was selected for the Phase 3 studies based on the available PK/PD, efficacy, and safety data from the Phase 1 first-in-human study (X2101) and the Phase 2 studies in patients with PNH, studies X2201 and X2204.

6.3 Efficacy

The pivotal Phase 3 study APPLY-PNH is a randomised, open-label, multicentre, active-comparator trial which included 97 adult patients with PNH with residual anaemia (haemoglobin < 10g/dL) despite

receiving a stable regimen of anti-C5 antibody therapy (eculizumab or ravulizumab) for at least 6 months prior to randomisation. Patients received iptacopan monotherapy 200 mg b.i.d. (n=62) or continued their anti-C5 regimen (n=35) for 24 weeks (randomised treatment period). The randomised treatment period was followed by a 24-week extension period, in which patients from the standard arm switched to iptacopan treatment, and patients from the experimental arm continued their treatment. After completion of the treatment extension period, patients were given the option to continue iptacopan treatment in the roll-over extension programme (REP) to evaluate long-term safety, tolerability, and efficacy. The primary objective was to demonstrate a superior haematological response on iptacopan treatment by (1) a sustained increase in haemoglobin levels of ≥ 2 g/dL from baseline in the absence of RBC transfusion (binary variable, success defined as 3 out of 4 measurements in Weeks 18 to 24 showing an increase ≥ 2 g/dL); (2) sustained haemoglobin levels ≥ 12 g/dL in the absence of RBC transfusion (binary variable, success defined as 3 out of 4 measurements in Weeks 18 to 24 showing an Hgb level ≥ 12 g/dL). Secondary endpoints included change from baseline Hgb levels, change in FACIT-fatigue scores, transfusion avoidance, occurrence of breakthrough haemolysis (BTH), and LDH levels. According to statistical planning for APPLY-PNH, the primary and secondary endpoints were tested using sequentially rejective graphical procedures, with an overall study 1-sided Type I error of 0.025 to ensure the control of Type I error when first testing the 2 primary endpoints and subsequently testing secondary endpoints following the pre-defined scheme for multiplicity adjustment. Patients were randomised in an 8:5 ratio to receive either iptacopan monotherapy for 24 weeks or continue with their established C5i regimen.

Randomisation was stratified by the type of C5i (eculizumab or ravulizumab) and by the transfusion history of the past 6 months (transfusion received yes vs no).

Demographics and baseline disease characteristics were fairly balanced between the treatment arms. There were slightly more patients ≥75 years of age in the iptacopan arm (10% vs 3%) and the median number of transfusions in the 6 months prior to randomisation was 2.0 in both arms. In both arms, there were more female than male participants (31% male vs 69% female overall). Overall, the majority of patients were White (76%) or Asian (20%), and 4% were Black or African American (see Section 5.3.3.1.4).

For the primary endpoint sustained increase in haemoglobin levels from the baseline of ≥ 2 g/dL between Week 18 and Week 24, the marginal proportion (95% CI) was 82.3% (73.4, 90.2) in the iptacopan group and significantly higher than the proportion of 2.0% (1.1, 4.1) in the anti-C5 group. For the primary endpoint sustained haemoglobin levels of ≥ 12 g/dL in Week 18-24, the marginal proportion was 68.8% (58.3, 78.9) in the iptacopan group and significantly higher than the proportion of 1.8% (0.9, 4.0) in the anti-C5 group. The sensitivity analyses conducted by the applicant support the robustness of the primary results.

Pre-specified subgroup analyses (baseline Hgb < or ≥9 g/dl, age < or ≥45 years, time since diagnosis < or ≥5 years, transfusion incidents in the 6 months prior to randomisation < or ≥2, C5i: eculizumab or ravulizumab) were all in favour of iptacopan.

The efficacy analyses for the following pre-specified secondary endpoints were in favour of iptacopan treatment: transfusion avoidance, change from baseline haemoglobin, change from baseline reticulocyte counts, change from baseline FACIT-fatigue score, and rate of clinical BTH. No significant treatment difference was observed for the secondary endpoints change from baseline LDH and rate of major adverse vascular events (MAVEs).

6.4 Safety

The iptacopan PNH safety pool comprises 170 patients, and additional safety information is provided from the renal pool with 53 patients. In the PNH pool, approximately 9 out of 10 patients experienced any grade TEAE, and 1 out of 10 patients experienced a severe TEAE (mostly SAEs). The most common any grade TEAEs included infections, headache, diarrhoea, and arthralgia. SAEs included haemolysis, infections, and neoplasms. The rate of malignant neoplasms in the PNH pool warrants further observation. Cases of severe thrombocytopenia on iptacopan treatment were reported in the PNH pool. In the PNH pool, 3 deaths were reported, all of which occurred in the Phase 2 study X2201, in which iptacopan was supplied as add-on treatment to existing C5 inhibitor treatment. The requested indication is for iptacopan monotherapy, and no deaths were reported in the PNH studies testing iptacopan monotherapy. Additionally, 1 death was reported in the renal pool. However, the narrative provided does not suggest a relation to iptacopan treatment.

6.5 Final clinical benefit-risk assessment

Efficacy data from APPLY-PNH in PNH patients with clinical signs of haemolysis on C5 inhibitor treatment is convincing (increase of Hgb level ≥2 g/dl compared to baseline: 82.3% in iptacopan group vs 2.0% in the anti-C5 group; haemoglobin levels of ≥ 12 g/dL in Week 18-24: 68.8% vs 1.8%). The safety profile of iptacopan is in line with other complement inhibitors and the overall small patient number is considered acceptable in view of the rarity of the disease. The benefit-risk assessment is considered positive for iptacopan monotherapy in patients with ongoing, clinically relevant haemolysis despite C5 inhibitor therapy.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Fabhalta capsules was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the “Adverse effects” section for advice on the reporting of adverse reactions.

FABHALTA®

Composition

Active substances

Iptacopan as iptacopan hydrochloride monohydrate

Excipients

Capsule contents: None.
Capsule shell: Gelatin, red iron oxide (E172), titanium dioxide (E171) and yellow iron oxide (E172).
Printing ink: Black iron oxide (E172), concentrated ammonia solution (E527), propylene glycol (E1520), potassium hydroxide (E525) and shellac (E904).

Pharmaceutical form and quantity of active substance per unit

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

Indications/Potential uses

Fabhalta is indicated as monotherapy for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have had an inadequate response despite at least 6 months of treatment with a C5 inhibitor (see “Clinical efficacy”).

Dosage/Administration

Usual dosage

The recommended dose is 200 mg orally twice daily.
If a dose or doses are missed, the patient should be instructed to take one dose of iptacopan as soon as possible (even if it is shortly before the next scheduled dose) and then to resume the regular dosing schedule.

Duration of treatment

PNH is a disease that requires chronic treatment. Discontinuation of this medicinal product is not recommended unless clinically indicated (see “Warnings and precautions”).

Switching from C5 inhibitors (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 eculizumab dose.

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

Switching from other PNH therapies to iptacopan has not been studied.

Adherence to dosing schedule

Patients with PNH should be made aware of the importance of adherence to the dosing schedule in order to minimise the risk of haemolysis (see “Warnings and precautions”).

Patients with hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The use of iptacopan is not recommended in patients with severe hepatic impairment (Child-Pugh class C) (see “Pharmacokinetics”).

Patients with renal impairment

No dose adjustment is required in patients with mild (estimated glomerular filtration rate [eGFR] 60 to <90 ml/min/1.73 m^2) or moderate (eGFR 30 to <60 ml/min/1.73 m^2) renal impairment. The use of iptacopan is not recommended in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) with or without haemodialysis (see “Pharmacokinetics”).

Elderly patients

Although no obvious age-related differences were observed in clinical studies and there is no evidence that special precautions are needed when treating elderly people, the number of patients over 65 years of age was insufficient to determine whether there are age-related differences (see “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of iptacopan have not been demonstrated in patients under 18 years of age.

Method of administration

For oral use. Iptacopan can be taken with or without food (see “Pharmacokinetics”). The capsules must be swallowed whole and must not be opened, broken or chewed.

Contraindications

Iptacopan is contraindicated:

- in patients with hypersensitivity to iptacopan or any of the other excipients.
- in patients who are not currently vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae* unless the risk of delaying iptacopan treatment outweighs the risk of infection with these encapsulated bacteria (see “Warnings and precautions”).
- for initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis* or *Haemophilus influenzae* type B.

Warnings and precautions

Serious infections caused by encapsulated bacteria

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 available. Refer to local vaccination recommendations.
Vaccines should be administered at least 2 weeks prior to administration of the first dose of iptacopan. If iptacopan treatment must be initiated prior to vaccination, patients should be vaccinated as soon as possible and receive antibiotic prophylaxis until 2 weeks after vaccination.
If necessary, patients may be revaccinated in accordance with local vaccination recommendations.
Vaccination reduces, but does not eliminate, the risk of serious infection. Serious infection may rapidly become life-threatening or even 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 “Adverse effects”).

Monitoring of PNH manifestations after iptacopan discontinuation

If iptacopan 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 elevated lactate dehydrogenase (LDH) levels along with a sudden decrease in haemoglobin levels or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, major adverse vascular events (MAVEs; including thrombosis), dysphagia or erectile dysfunction. If discontinuation of iptacopan is necessary, alternative therapy should be considered.
If haemolysis occurs after discontinuation of iptacopan, restarting iptacopan treatment should be considered.

Educational materials

All physicians who intend to prescribe Fabhalta must ensure they have received and are familiar with the guidelines for healthcare professionals. Physicians must discuss the benefits and risks of Fabhalta treatment with the patient and provide them with the patient guidelines and patient card. The patient should be instructed to seek prompt medical care if any signs or symptoms of serious infection occur during Fabhalta therapy, particularly if these indicate an infection with encapsulated bacteria.

Interactions

Influence of other substances on iptacopan pharmacokinetics

Iptacopan is a substrate for CYP2C8, P-gp, BCRP, MRP2 and OATP1B1/1B3 (see "Pharmacokinetics").

When co-administered with clopidogrel (a moderate CYP2C8 inhibitor), iptacopan C_{max} and AUC increased by 5% and 36%, respectively.
Co-administration of strong CYP2C8 inhibitors (e.g. gemfibrozil) may increase iptacopan exposure, which may lead to an increased risk of adverse reactions with iptacopan. Co-administration with a strong CYP2C8 inhibitor is not recommended.
Co-administration of strong inducers of CYP2C8, UGT1A1, P-gp, BCRP and OATP1B1/3 such as rifampicin may decrease iptacopan exposure, which may lead to a loss of or decrease in the efficacy of Fabhalta. Monitor the clinical response and discontinue use of the inducer if a loss of Fabhalta efficacy is determined.

When co-administered with ciclosporin (an OATP1B1/1B3, P-gp and BCRP inhibitor), iptacopan C_{max} and AUC increased by 41% and 50%, respectively.

Influence of iptacopan on the pharmacokinetics of other substances

In vitro, iptacopan does not inhibit common cytochrome P450 enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5) or induce CYP1A2, 2B6 or 2C9 at clinically relevant concentrations.
In vitro data showed that iptacopan has the potential for time-dependent inhibition of CYP2C8 and may increase the exposure of sensitive CYP2C8 substrates such as repaglinide, dasabuvir or paclitaxel. Co-administration of iptacopan and sensitive CYP2C8 substrates has not been studied clinically. Caution is required if co-administration of iptacopan with sensitive CYP2C8 substrates is necessary.
In vitro data showed that iptacopan has the potential for induction of CYP3A4 and may decrease the exposure of sensitive CYP3A4 substrates. Co-administration of iptacopan and sensitive CYP3A4 substrates has not been studied clinically. Caution is required if co-administration of iptacopan with sensitive CYP3A4 substrates is necessary, especially for those with a narrow therapeutic index (e.g. carbamazepine, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

In vitro, iptacopan is an inhibitor of OATP1B1 and P-gp. Iptacopan does not inhibit the transporters MATE1, MATE2-K, OAT1, OAT3, OATP1B3, OCT1 or OCT2.

In the presence of iptacopan, the C_{max} of digoxin (a P-gp 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.

Proven or potential interactions between iptacopan and other medicinal products:

Co-medications (enzymes or transporters)	Co-medication dose	Iptacopan dose	Geometric mean ratios (90% CI)	
			C_{max}	AUC_{inf}
Influence of other medicinal products on iptacopan				
Clopidogrel (moderate CYP2C8 inhibitor)	300 mg once on day 6 then 75 mg once daily from day 7 to day 10	100 mg once daily on day 1 and day 7	1.05 (0.97, 1.14)	1.36 (1.28, 1.45)
Ciclosporin (OATP1B1/1B3, P-gp, BCRP inhibitor)	175 mg twice daily from day 6 to day 9	100 mg once daily on day 1 and day 6	1.41 (1.35, 1.47)	1.50 (1.42, 1.59)
Influence of iptacopan on other medicinal products				
Digoxin (P-gp substrate)	0.25 mg once daily on day 1 and 0.25 mg once daily on day 17	200 mg twice daily from day 12 to day 26	1.08 (0.94, 1.24)	1.02 (0.93, 1.12)
Rosuvastatin (OATP substrate)	10 mg once daily on day 1 and 10 mg once daily on day 17	200 mg twice daily from day 12 to day 26	1.00 (0.87, 1.15)	1.01 (0.91, 1.12)

Pregnancy/Breast-feeding

Pregnancy

There are no or only a limited amount of data on the use of iptacopan in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see “Preclinical data”).
As a precaution, use of iptacopan during pregnancy should be avoided.

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

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.

Breast-feeding

It is not known if iptacopan is transferred into human milk after oral administration. There are no data on the effects of iptacopan on the breast-fed infant or milk production.
The developmental and health benefits of breast-feeding for the child should be considered along with the mother's clinical need for iptacopan and any potential adverse effects (e.g. serious infections caused by encapsulated bacteria) on the breast-fed child from iptacopan or from the underlying maternal condition.

Fertility

There are no data on the influence of iptacopan on human fertility. Available preclinical data do not suggest an effect of iptacopan treatment on fertility (see "Preclinical data").

Effects on ability to drive and use machines

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

Adverse effects

Summary of the safety profile

The safety profile of iptacopan is based on the analysis of pooled safety data from 298 patients with PNH (N=174) or renal disease (N=124) treated in multiple studies with iptacopan at any dosage. The median duration of iptacopan exposure was 14.1 months. The most commonly reported adverse effects in patients treated with iptacopan were upper respiratory tract infection (25.5%), headache (18.1%), abdominal pain (12.8%) and diarrhoea (10.1%).

List of adverse effects

Adverse effects are listed by MedDRA system organ class and frequency according to 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), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 Adverse effects from clinical studies in patients treated with iptacopan

MedDRA system organ class	**Adverse effects**	**Pool of iptacopan studies* N=298 n (%)**	**Frequency category**
Blood and lymphatic system disorders	Decreased platelet count[1]	14 (4.7)	Common

MedDRA system organ class	Adverse effects	Pool of iptacopan studies* N=298 n (%)	Frequency category
Gastrointestinal disorders	Abdominal pain[2]	38 (12.8)	Very common
	Diarrhoea	30 (10.1)	Very common
	Nausea	24 (8.1)	Common
Infections and infestations	Upper respiratory tract infection[3]	76 (25.5)	Very common
	Bacterial pneumonia[7]	5 (1.7)	Common
	Urinary tract infection[4]	18 (6.0)	Common
	Bronchitis[5]	9 (3.0)	Common
Musculoskeletal and connective tissue disorders	Arthralgia	19 (6.4)	Common
Nervous system disorders	Headache[6]	54 (18.1)	Very common
	Dizziness	15 (5.0)	Common
Skin and subcutaneous tissue disorders	Urticaria	1 (0.3)	Uncommon

*Patients with PNH (N=174) or renal disease (N=124) treated in multiple studies with iptacopan at any dosage.

[1]Decreased platelet count includes preferred terms thrombocytopenia and decreased platelet count.

[2]Abdominal pain includes preferred terms abdominal pain, upper abdominal pain, abdominal tenderness and abdominal discomfort.

[3]Upper respiratory tract infection includes preferred terms sinusitis, influenza, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection and viral upper respiratory tract infection.

[4]Urinary tract infection includes preferred terms pseudomonal urinary tract infection, asymptomatic bacteriuria, cystitis and cystitis escherichia.

[5]Bronchitis includes preferred terms bronchitis, haemophilus bronchitis, bacterial bronchitis and tracheobronchitis.

[6]Headache includes preferred terms headache and head discomfort.

[7]Bacterial pneumonia includes preferred terms bacterial pneumonia and pneumococcal pneumonia.

Description of specific adverse effects and additional information

Infections (all indications)

In clinical studies on PNH and renal disease 4 out of 298 patients (1.3%) reported serious bacterial pneumonia during iptacopan treatment (2 patients with PNH had bacterial pneumonia and 2 patients

with renal disease had pneumococcal pneumonia). All patients were vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B and recovered following treatment with antibiotics. Patients with PNH were treated with iptacopan throughout the treatment.

Decreased platelet count (only in patients with PNH)

A decrease to CTCAE grade 1 (based on CTCAE version 4.03) was observed in 50% of patients with a normal baseline platelet count. Patients who regressed to grade 3 (3% of patients) or grade 4 (4% of patients) had pre-existing thrombocytopenia or relevant co-morbidities such as myelodysplastic syndrome, aplastic anaemia, COVID-19 and immune thrombocytopenia.

Laboratory and vital signs

Increased cholesterol levels and blood pressure (only observed in patients with PNH)

In patients treated with 200 mg iptacopan twice daily in PNH clinical studies, mean increases from baseline of approximately 0.75 mmol/l were seen at month 6 for total cholesterol and LDL-cholesterol. Mean values remained within the normal ranges. An increase in blood pressure, particularly diastolic blood pressure (DBP), was observed (mean increase 4.4 mmHg at month 6). The mean DBP did not exceed 80 mmHg. The increase in total cholesterol, LDL-C and DBP correlated with an increase in haemoglobin (improvement in anaemia) in patients with PNH (see “Properties/Actions”).

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal ElViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

Limited data are available with regard to overdose in humans. During clinical studies a few patients took up to 800 mg iptacopan daily, which was well tolerated. In healthy volunteers the highest dose was 1,200 mg administered as a single dose, which was well tolerated.

Treatment

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

Properties/Actions

ATC code

L04AJ08

Mechanism of action

Iptacopan is a proximal complement inhibitor that binds to Factor B (FB) to selectively inhibit the alternative pathway. 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 C3b opsonisation. 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 alternative pathway biomarkers, Wieslab assay and plasma Bb (fragment Bb of FB), was ≤2 hours after a single iptacopan dose in healthy volunteers.
In PNH patients receiving concomitant C5 inhibitor treatment and 200 mg iptacopan twice daily, Wieslab 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 200 mg iptacopan twice daily.
In PNH patients receiving concomitant C5 inhibitor treatment and 200 mg iptacopan twice daily, the mean PNH red blood cell (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 200 mg iptacopan twice daily achieved a reduction of LDH levels to <1.5 times the upper limit of normal (ULN) after 13 weeks and maintained the effect through to the end of the study. In treatment-naïve PNH patients, 200 mg iptacopan twice daily reduced LDH levels 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 resulted in >4-fold peak concentrations versus the 200 mg twice daily dosage) showed no effect on cardiac repolarisation or QT interval.

Clinical efficacy

The efficacy and safety of iptacopan in adult patients with PNH were evaluated in a multicentre, open-label, active comparator-controlled, 24-week phase III study (APPLY-PNH; NCT04558918).

The APPLY-PNH study enrolled adult PNH patients with residual anaemia (haemoglobin <10 g/dl) despite previous treatment with a stable regimen of C5 inhibitor treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomisation.

97 patients were randomised in an 8:5 ratio either to receive 200 mg iptacopan orally twice daily (n=62) or C5 inhibitor 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 C5 inhibitor treatment and transfusion history within the last 6 months. Following completion of the 24-week RCP all patients were given the opportunity to enrol in a 24-week treatment extension period and receive iptacopan monotherapy. Subsequently, patients could participate in a separate long-term extension study.

Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 2).

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

Table 2 Patient baseline demographics and characteristics in APPLY-PNH study

Parameters	**Statistics**	**Iptacopan (N=62)**	**C5 inhibitors (N=35)**
Age (years)	Mean (SD) min, max	51.7 (16.9) 22, 84	49.8 (16.7) 20, 82
Gender Female	 n (%)	 43 (69.4)	 24 (68.6)
Haemoglobin level (g/dl)	Mean (SD)	8.9 (0.7)	8.9 (0.9)
TOTAL PNH RBC clone size (type II + III) (%)	Mean (SD)	64.6 (27.5)	57.4 (29.7)
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 randomisation	n (%)	35 (56.5)	21 (60.0)
Number of transfusions in 6 months prior to randomisation among patients who had a transfusion	Mean (SD)	3.1 (2.6)	4.0 (4.3)
History of MAVEs (including thrombosis) in last 12 months	n (%)	12 (19.4)	10 (28.6)

Parameters	Statistics	Iptacopan (N=62)	C5 inhibitors (N=35)
Disease duration (years)	Mean (SD)	11.9 (9.8)	13.5 (10.9)
Duration of prior anti-C5 treatment (years)	Mean (SD)	3.8 (3.6)	4.2 (3.9)
Abbreviations: LDH, lactate dehydrogenase; MAVEs, major adverse vascular events; RBC, red blood cell; SD, standard deviation			

Efficacy was determined based on two primary endpoints that aimed to demonstrate superiority of iptacopan to C5 inhibitors in achieving a haematological response after 24 weeks of treatment without the need for transfusion. For this purpose, the proportion of patients demonstrating a response was assessed: 1) increase of ≥2 g/dl in haemoglobin levels from baseline (haemoglobin improvement) and/or 2) stabilised haemoglobin levels ≥12 g/dl. Secondary endpoints included transfusion avoidance, change from baseline in haemoglobin levels, change from baseline in FACIT-Fatigue score, occurrence of clinical breakthrough haemolysis and change from baseline in absolute reticulocyte counts.

Iptacopan was superior to C5 inhibitor treatment, with a significant difference in response rate of 80.3% (82.2% vs 2%) for haemoglobin improvement (sustained increase of haemoglobin levels ≥2 g/dl from baseline) and 67% (68.8% vs 1.8%) for stabilised 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).

Iptacopan was also statistically superior to the anti-C5 group for some clinically relevant secondary endpoints: for transfusion avoidance rate, with a treatment difference of 68.9% (94.8% vs 25.9% ($p<0.0001$)), and for change from baseline in haemoglobin level (treatment difference of +3.66 g/dl; $p<0.0001$). The treatment effect of iptacopan was also observed in Functional Assessment of Chronic Illness Therapy (FACIT) scores and absolute reticulocyte counts (ARCs) (treatment difference of -116.2 x 10^9/l; $p<0.0001$). The treatment effect of iptacopan on haemoglobin was seen as early as day 7 and was sustained during the study.

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

Endpoints	Iptacopan (N=62)	C5 inhibitor (N=35)	Difference (95% CI) p-value
Primary endpoints			
Number of patients achieving improvement in haemoglobin levels (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 in the absence of transfusions[a] Response rate[c] (%)	42/60[b] 68.8	0/35[b] 1.8	 67.0 (56.4, 76.9) <0.0001

Abbreviations: LDH, lactate dehydrogenase; MAVEs, major adverse vascular events

[a,b,c] Assessed between day 126 and 168[(a)], 14 and 168 [(b)] and 1 and 168 [(c)].

[a] Assessed between day 126 and 168.

[b] Based on observed data among evaluable patients.

[c] Response rate reflects the adjusted proportion.

The results for the primary endpoints were consistent across the predefined subgroups studied.

Pharmacokinetics

Absorption

Following oral administration iptacopan reached peak plasma concentrations approximately 2 hours post dose. At the recommended dosage 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 (see "Dosage/Administration").

Distribution

Iptacopan showed concentration-dependent plasma protein binding due to binding to FB in the systemic circulation. Iptacopan was 75% to 93% protein bound *in vitro* at the relevant clinical plasma concentrations. After administration of 200 mg iptacopan 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 metabolised oxidatively. Metabolism of iptacopan includes N-dealkylation, O-deethylation, oxidation and dehydrogenation, mostly driven by CYP2C8 (98%) and to a minor extent by CYP2D6 (2%). Glucuronidation (UGT1A1, UGT1A3, UGT1A8) plays a minor role in metabolism. 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.

Elimination

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 a 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 the faeces. The clearance of iptacopan at steady state is 7.96 l/h after administration of 200 mg iptacopan twice daily. The half-life ($t_{1/2}$) of iptacopan at steady state is approximately 25 hours after administration of 200 mg iptacopan twice daily.

Linearity/non-linearity

At a dosage of between 25 mg and 200 mg twice daily iptacopan was overall less than dose proportional. At doses of 100 mg and 200 mg, iptacopan exposure increased in an approximately dose-proportional manner. Non-linearity was primarily attributed to the saturable binding of iptacopan to its target FB in plasma.

Pharmacokinetics in special populations

A population pharmacokinetic (PK) analysis was conducted on data from 234 patients. Age (18-84 years), body weight (34.9-120 kg), eGFR (27.45-142.76 ml/min/1.73 m^2), ethnicity and gender did not significantly influence iptacopan PK. Studies that included Asian subjects showed that the PK of iptacopan were similar to white subjects.

Hepatic impairment

Based on a study in patients with mild, moderate or severe hepatic impairment, a negligible effect on the total exposure (bound and unbound) of iptacopan was observed. An approximately 1.04-fold increase in iptacopan C_{max} was observed in patients with mild hepatic impairment (Child-Pugh A, n=8), while no changes were observed in patients with moderate (Child-Pugh B, n=8) or severe (Child-Pugh C, n=6) hepatic impairment. The increase in AUC_{inf} in patients with mild and severe hepatic impairment was 1.03-fold, while there was no change in patients with moderate hepatic impairment.
Unbound iptacopan C_{max} increased 1.4-, 1.7- and 2.1-fold, and unbound iptacopan AUC_{inf} increased 1.5-, 1.6- and 3.7-fold in patients with mild, moderate and severe hepatic impairment, respectively. No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (see “Dosage/Administration”).

Renal impairment

Only 17.9% of iptacopan was excreted in the urine as parent drug. The kidney is therefore a minor route of elimination. The effects of renal impairment on the clearance of iptacopan were 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 to <90 ml/min/1.73 m^2) or moderate (eGFR 30 to <60 ml/min/1.73 m^2) renal impairment and no dose adjustment is required (see “Dosage/Administration”). Patients with severe renal impairment or dialysis patients have not been studied.

Preclinical data

Safety pharmacology

In dogs, upon treatment initiation a dose-dependent heart rate increase and blood pressure decrease were observed. The magnitude of the heart rate changes decreased with time and the effect was not considered adverse up to 150 mg/kg/day (equivalent to ~14-fold the MRHD based on AUC and ~19-fold based on C_{max}). In cynomolgus monkeys QTc prolongation was observed following single administration of ≥300 mg/kg iptacopan (equivalent to ≥21-fold the MRHD based on C_{max}).
No iptacopan-related effects on the respiratory or nervous system were identified in rats.

Repeated-dose toxicity

The preclinical safety profile of iptacopan was assessed in rats at oral doses up to 750 mg/kg/day (~7-fold the MRHD based on AUC) for 26 weeks and in dogs at oral doses up to 150 mg/kg/day (~14-fold the MRHD based on AUC) for 39 weeks. Adverse and irreversible findings in the chronic toxicity studies were limited to bone marrow fibrosis and dyserythropoiesis in one dog at the highest

dose. Reversible and non-serious findings included thyroid follicular cell hypertrophy and testicular tubular degeneration.
Adverse cardiac effects (e.g. cell degeneration and fibrosis) were observed in dogs at doses ≥300 mg/kg/day (equivalent to >39-fold the MRHD based on AUC). These were only administered in studies with a treatment duration of up to 4 weeks.

Mutagenicity and carcinogenicity

Iptacopan was not genotoxic in a battery of *in vitro* and *in vivo* assays. Carcinogenicity studies conducted with iptacopan in mice and rats after 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.

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) 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 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.
In the embryofetal development study in rats iptacopan administered orally during organogenesis did not induce adverse maternal, embryo or fetal toxicity up to the highest dose of 1,000 mg/kg/day, which corresponds to 5-fold the MRHD based on AUC. Non-adverse findings in rats included fetal skull ossification delays and benign cysts on the left side of the parietal region of the head, with no impact on skull, brain, or any other head-based structure, and were observed in only two fetuses in 1 out of 22 litters at 1,000 mg/kg/day.
In the embryofetal development study in rabbits iptacopan did not induce embryo or fetal toxicity at any dose administered orally, while maternal toxicity was observed due to adverse body weight loss and reduced food consumption in the pregnant animals at the highest dose of 450 mg/kg/day, which corresponds to 8-fold the MRHD based on AUC.
In the pre- and postnatal development study in rats, in which iptacopan was 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 and offspring up to the highest dose tested of 1,000 mg/kg/day (~5-fold the MRHD based on AUC).

Other information

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Do not store above 30°C.
Store in the original pack to protect the contents from moisture.
Keep out of the reach of children.

Swissmedic number

68603

Pack sizes

200 mg Fabhalta: Pack containing 56 hard capsules [A]

Marketing authorisation holder

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