swissmedic

Date: 14 November 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Fabhalta

International non-proprietary name:	iptacopan as iptacopan hydrochloride monohydrate
Pharmaceutical form:	capsule
Dosage strength(s):	200 mg
Route(s) of administration:	oral use
Marketing authorisation holder:	Novartis Pharma Schweiz AG
Marketing authorisation no.:	68603
Decision and decision date:	extension of therapeutic indication approved on 25 September 2025

Note:

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

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

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
C3G	Complement 3 glomerulopathy
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
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
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RAS	Renin-angiotensin system
RMP	Risk management plan
SAE	Serious adverse event
sC5b-9	Soluble complement 5b-9
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
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) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 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 complement 3 glomerulopathy (C3G).

2.2.2 Approved indication

Fabhalta is indicated to treat adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are intolerant to RAS inhibitors or for whom a RAS inhibitor is contraindicated (see "Clinical efficacy").

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	15 April 2025
Formal control completed	23 April 2025
Preliminary decision	25 July 2025
Response to preliminary decision	21 August 2025
Final decision	25 September 2025
Decision	approval

3 Medical context

Complement 3 glomerulopathy (C3G) is a rare kidney disease caused by dysregulation of the complement system as part of the immune system, resulting in accumulation of complement 3 proteins in the renal glomeruli. The glomerulus is the principal filtering unit of the kidney.

Clinical manifestations of C3G may be preceded by urinary abnormalities such as proteinuria and/or haematuria, nephrotic syndrome, arterial hypertension, peripheral oedema, or fatigue. These symptoms may be accompanied by a variable degree of renal function impairment, with complement abnormalities such as low C3 levels and/or elevated serum levels of sC5b-9. Diagnosis of C3G is established by renal biopsy showing the characteristic findings on immunofluorescence microscopy.

Due to the rarity of C3G disease, which has an incidence of 1-2 per 1 million people, there are only very limited data on natural progression and prognosis for C3G. About half of patients with C3G develop renal failure within 10 years of diagnosis. Treatment of C3G has 2 goals: to support renal function and to suppress immune system activity.

4 Nonclinical aspects

The applicant did not submit any new nonclinical studies to support the requested new indication, which is considered acceptable. The new indication is unlikely to result in any significant risk to the environment. From the nonclinical point of view, there are no objections to the approval of the new indication applied for.

5 Clinical aspects

The available assessment report from the EMA and respective product information from the EMA and FDA were used as a basis for the clinical and clinical pharmacology evaluation. The clinical aspects in this SwissPAR refer to the publicly available EMA assessment report EMA/96410/2025 for Fabhalta, published 11 April 2025, Procedure No. EMEA/H/C/005764/II/0001.

6 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.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Fabhalta 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 side effect. See the “Adverse effects” section for advice on the reporting of side effects.

FABHALTA®

Composition

Active substance

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”).
- Fabhalta is indicated to treat adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor or in patients who are intolerant to RAS inhibitors or for whom a RAS inhibitor is contraindicated (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 and C3G are diseases that require chronic treatment. Discontinuation of this medicinal product is not recommended unless clinically indicated.

Switching PNH patients 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

All patients should be made aware of the importance of adherence to the dosing schedule. In patients with PNH, adherence to therapy is important 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 is 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 embryonic/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. Complement 3 glomerulopathy during pregnancy may be associated with adverse maternal outcomes, particularly pre-eclampsia and miscarriage, as well as adverse fetal outcomes, including preterm birth and low birth weight.

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 372 patients with PNH (N=174) or renal disease (N=198) treated in multiple studies with iptacopan at any dosage. The median duration of iptacopan exposure was 14.2 months. The most commonly reported adverse effects in patients treated with iptacopan were upper respiratory tract infection (25.8%), headache (19.1%), abdominal pain (11.3%) and diarrhoea (12.1%).

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=372 n (%)	Frequency category
Infections and infestations	Upper respiratory tract infection[3]	96 (25.8)	Very common
	Bacterial pneumonia[7]	6 (1.6)	Common
	Urinary tract infection[4]	22 (5.9)	Common
	Bronchitis[5]	10 (2.7)	Common
	Pneumococcal infection[8]	3 (0.8)	Uncommon
Blood and lymphatic system disorders	Decreased platelet count[1]	14 (3.8)	Common
Nervous system disorders	Headache[6]	60 (16.1)	Very common
	Dizziness	16 (4.3)	Common
Gastrointestinal disorders	Abdominal pain[2]	42 (11.3)	Very common
	Diarrhoea	36 (9.7)	Common
	Nausea	27 (7.3)	Common
Skin and subcutaneous tissue disorders	Urticaria	1 (0.3)	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	19 (5.1)	Common

* Patients with PNH (N=174) or renal disease (N=198) 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, lower abdominal pain, upper abdominal pain, abdominal tenderness and abdominal discomfort.

[3]Upper respiratory tract infection includes preferred terms acute 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.

MedDRA system organ class	Adverse effects	Pool of iptacopan studies* N=372 n (%)	Frequency category
[8]Pneumococcal infection includes preferred terms pneumococcal sepsis and pneumococcal pneumonia.			

Description of specific adverse effects and additional information

Infections (all indications)

In clinical studies on PNH and renal disease 5 out of 372 patients (1.3%) reported serious bacterial pneumonia during iptacopan treatment (2 patients with PNH had bacterial pneumonia and 3 patients with renal disease had pneumococcal pneumonia, including 1 patient who also reported pneumococcal sepsis). 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”).

In patients treated with 200 mg iptacopan twice daily in the C3G clinical trial, no clinically relevant differences in total cholesterol, LDL cholesterol or blood pressure were observed compared to placebo.

Reporting suspected side effects after marketing 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 side effects via the online portal EIViS (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 C3b-mediated EVH and terminal complement-mediated IVH.
In C3G, overactivation of the alternative complement pathway leads to C3 cleavage within the glomeruli, resulting in C3 deposition and inflammation, which are responsible for the pathogenesis of C3G and can lead to kidney damage and ultimately kidney failure. By binding to factor B, iptacopan selectively inhibits the activity of the alternative complement pathway, resulting in reduced C3 cleavage and decreased C3 deposition in the kidney.

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.
In patients with C3G, the mean serum C3 level increased by 249% compared to baseline on day 14 of iptacopan treatment, indicating inhibition of pathological C3 cleavage. Plasma-soluble C5b-9 (also known as membrane attack complex (MAC)) and urine-soluble C5b-9 decreased by 71.8% and 92.1%, respectively, from baseline at the first observation on day 30 of treatment with 200 mg iptacopan twice daily. This effect was sustained over the 6-month observation period. In patients with recurrent C3G after kidney transplantation, the mean serum C3 level doubled from baseline to reach the normal range by day 28 of iptacopan treatment and remained stable during the follow-up period of up to 39 months. A reduction in glomerular C3 deposition, as measured by changes in C3 deposition scores, was also observed in patients with native kidney C3G and in those with recurrent C3G after kidney transplantation.

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

Paroxysmal nocturnal haemoglobinuria (PNH)
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)
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)	51/60[b]	0/35[b]	
Response rate[c] (%)	82.3	2.0	80.2 (71.2, 87.6) <0.0001

Endpoints	Iptacopan (N=62)	C5 inhibitor (N=35)	Difference (95% CI) p-value
Number of patients achieving sustained haemoglobin level ≥12 g/dl in the absence of transfusions[a]	42/60[b]	0/35[b]	
Response rate[c] (%)	68.8	1.8	67.0 (56.4, 76.9) <0.0001

Abbreviations: RR, rate ratio; 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 follow-up data from evaluable patients.

[c] Response rate reflects the adjusted proportion.

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

Complement 3 glomerulopathy

APPEAR-C3G

APPEAR-C3G, a multicenter, randomised, double-blind, placebo-controlled study, enrolled 74 adult patients with biopsy-confirmed C3G, UPCR ≥1 g/g and an eGFR ≥30 ml/min/1.73 m^2.

Patients were randomised (1:1) to receive either 200 mg iptacopan orally twice daily (n=38) or placebo (n=36) for 6 months, followed by a 6-month open-label treatment period during which patients received 200 mg iptacopan orally twice daily. 73 patients completed the open-label treatment period.

Patients received a stable, maximum tolerated dose of a renin-angiotensin system (RAS) inhibitor. Randomisation was stratified according to whether or not patients were receiving concomitant immunosuppressive therapy (i.e., corticosteroids and/or mycophenolate mofetil/sodium (MMF/MPS)). All such therapies (i.e., RAS inhibitors, corticosteroids and MMF/MPS) had to be administered at stable doses for 90 days prior to randomisation and throughout the study.

Patients were required to be vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae*; they were also recommended to receive vaccination against *Haemophilus influenzae* type B. If a patient had not yet been vaccinated or required a booster vaccination, vaccination was to be administered at least 2 weeks prior to the first dose. If iptacopan treatment was initiated earlier than 2 weeks after vaccination, antibiotic prophylaxis was administered.

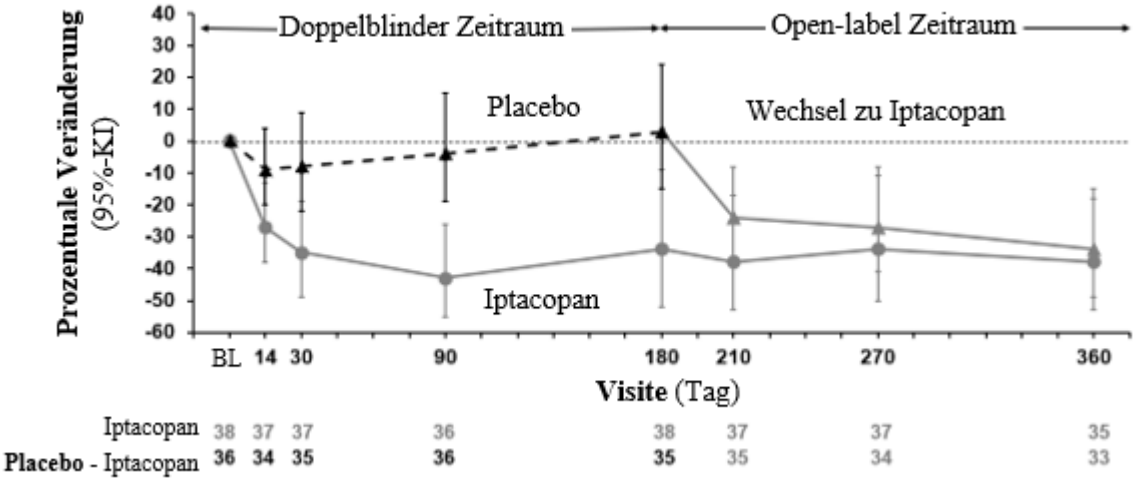
At baseline, patients had a mean age (standard deviation [SD]) of 26.1 (10.4) years (range 18-52) and 29.8 (10.8) years (range 18-60) in the iptacopan and placebo groups, respectively. At the time of C3G diagnosis, 40% (iptacopan) and 17% (placebo) of patients were <18 years old. Female patients comprised 29% (iptacopan) and 44% (placebo). The geometric mean UPCR was 3.33 g/g and 2.58 g/g in the iptacopan and placebo groups, respectively. The mean modelled pre-randomisation eGFR slope was -10.75 and -7.64 ml/min/1.73 m^2 per year in the iptacopan and placebo groups, respectively. The mean (SD) eGFR was 89.3 (35.2) ml/min/1.73 m^2 and 99.2 (26.9) ml/min/1.73 m^2 in the iptacopan and placebo groups, respectively. Subtypes included C3 glomerulonephritis (C3GN) in 68% (iptacopan) and 89% (placebo) of patients and dense deposit disease (DDD) in 23.7% (iptacopan) and 2.8% (placebo). A stable dose of immunosuppressive therapy with corticosteroids and/or MMF/MPS was used in 42% (iptacopan) and 47% (placebo) of patients.

The primary efficacy endpoint was the percentage change from baseline in 24-hour UPCR after 6 months of treatment.

Iptacopan was superior to placebo, with a statistically significant and clinically meaningful reduction in 24-hour UPCR of 35.1% (95% CI: 13.8%, 51.1%, 1-sided p-value=0.0014) from baseline compared to placebo after 6 months of treatment (-30.2% and +7.6% for iptacopan and placebo, respectively).

The effect of iptacopan on 24-hour UPCR was maintained through 12 months (-40.0% from baseline). In patients who switched from placebo to iptacopan during the 6-month open-label treatment period, 24-hour UPCR decreased by 31.0% from month 6 to month 12. The first morning void (FMV) UPCR curve is described in Figure 1. In a *post-hoc* analysis, treatment with iptacopan significantly reduced the proportion of patients with nephrotic-range proteinuria (defined as UPCR ≥3 g/g) compared to baseline. The percentage of patients with nephrotic-range proteinuria decreased from 55.3% at baseline to 31.6% and 36.8% in the iptacopan group at 6 and 12 months, respectively. The percentage of patients assigned to placebo who experienced nephrotic-range proteinuria increased from 30.6% at baseline to 41.7% at month 6. After switching to iptacopan treatment, the percentage of nephrotic patients decreased to 27.8% after 12 months.

Figure 1 Geometric mean percent change in FMV-UPCR from baseline to month 12 (APPEAR-C3G)



After 6 months of treatment with iptacopan, there was no worsening of eGFR compared to baseline. The mean change in eGFR from baseline was +1.30 ml/min/1.73 m^2 for iptacopan and -0.86 ml/min/1.73 m^2 for placebo. At 12 months, the mean change in eGFR from baseline was +0.44 ml/min/1.73 m^2 (95% CI: -3.76, 4.64) in the iptacopan group.

The efficacy of iptacopan in adults with C3G was demonstrated in an open-label, phase II study (X2202) in patients with native kidney C3G (N=16) and in patients with recurrent C3G after kidney transplantation (N=11) over 3 months. Twenty-six patients were enrolled in a rollover extension study, in which they received iptacopan for up to 39 months.

The mean UPCR and eGFR remained stable throughout the study in the 16 patients with native kidney C3G. Of the 10 patients with recurrent C3G after kidney transplantation, 2 discontinued due to worsening renal function. In the other 8 patients with recurrent C3G, eGFR and UPCR remained essentially constant until the end of the observation period (up to 48 months).

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 and 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, the pharmacokinetics of 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 was similar to that observed in 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 embryonic 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.

Marketing authorisation number

68603

Pack sizes

200 Mg Fabhalta: pack containing 56 hard capsules [A]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

July 2025