NOVARTIS

Regulatory Affairs

Drug generic name

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Iptacopan*
Product(s) concerned (brand name(s)):	*FABHALTA*
Document status:	*Final*
Version number of the RMP Public Summary:	*1.2*
Date of final sign off of the RMP Public Summary	*23-Sep-2024*

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “FABHALTA” is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “FABHALTA” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “FABHALTA”.

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I. The medicine and what it is used for

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

It contains iptacopan as the active substance and it is given as a 200 mg twice daily oral hard gelatin capsule.

Further information about the evaluation of FABHALTA's benefits can be found in FABHALTA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of FABHALTA, together with measures to minimize such risks and the proposed studies for learning more about FABHALTA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of FABHALTA, routine risk minimization measures are supplemented with aRMMs mentioned under relevant important risks, outlined in the next sections.

In addition to the risk minimization measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of FABHALTA is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of FABHALTA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of FABHALTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 – List of important risks and missing information

List of important risks and missing information	
Important identified risks	Infections caused by encapsulated bacteria
Important potential risks	Serious haemolysis following discontinuation of iptacopan Malignancies
Missing information	Use in pregnant patients Long-term safety (>2 years)

II B: Summary of important risks

Table 2 – Important identified risk: Infection caused by encapsulated bacteria

Evidence for linking the risk to the medicine	Individuals with deficiencies in Factor B have an increased risk of infections caused by encapsulated bacteria (*N. meningitidis* and *S. pneumoniae*) (Slade et al 2013, Gauthier et al 2021) and activation of the alternative complement pathway has been shown to be one of the innate immune defense mechanisms against pneumococcal infection during the early stage of acute otitis media in a mouse model (Li et al 2011). The membrane attack complex (MAC) plays a role in host defense against infections caused by *N. meningitidis* and patients who are deficient in C5, a terminal component of the complement pathways, experience recurrent infections caused by *N. meningitidis*. *In vitro* research has shown that the serological response to meningococcal infection (serum bactericidal activity) is markedly reduced after blockade of the terminal pathway with anti-C5 therapies such as eculizumab, which dramatically increases the risk of meningococcal infections in patients treated with C5 inhibitors (Soliris USPI 2020, Ultomiris USPI 2022), but is largely maintained during AP blockade (Konar and Granoff 2017, Ispasanie et al 2021). C5 inhibitors have no effect, however, on complement-mediated host defense against *Streptococcus pneumoniae* (opsonophagocytosis), since it occurs earlier in the complement pathway. C3 inhibitors, such as the recently approved

	pegcetacoplan, have been shown to have an effect on opsonophagocytosis against pneumococci *in vitro*, consistent with the types of infections observed in C3-deficient patients. The effect was greater than that seen with more selective inhibitors of Factor D or Factor B (Muri et al 2021). Infections caused, or likely to have been caused, by encapsulated bacteria have been observed in clinical studies in patients treated with iptacopan.
Risk factors and risk groups	Risk factors for infection include history of immunodeficiency diseases, history of recurrent infections, patients with diabetes, transplant patients, elderly patients and children. Other risk factors include: • Unvaccinated or incompletely vaccinated patients. • Patients with PNH-associated bone marrow failure (including aplastic anaemia PNH, myelodysplastic syndrome), due to neutropenia. • Immunosuppressive treatment (e.g., high-dose steroids, mycophenolate mofetil, cyclosporine, tacrolimus, B-cell depleting agents). • Individuals exposed to certain bacteria through work or travel .
Risk minimization measures	**Routine risk communication** Risk addressed in SmPC Sections: - Contraindications (Section 4.3) - Warning and Precautions (Section 4.4) - Undesirable Effects (Section 4.8) Risk addressed in Package Leaflet (PL) - Section 2 and 4 SmPC section 4.3 and 4.4 where advice is given on vaccination/prophylactic antibiotic requirements. - SmPC section 4.4 where recommendation for monitoring of early signs and symptoms of infections is given. Legal status: Prescription only medicine **Additional risk minimization measures:** • Healthcare professional guide • Patient/caregiver guide • Patient safety card • System for controlled access • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CLNP023C12001B CLNP023C12003, PASS in iptacopan-treated patients using registry data See section II.C of this summary for an overview of the post-authorization development plan.

Table 3 – Important potential risk: Serious haemolysis following discontinuation of iptacopan

Evidence for linking the risk to the medicine	This potential risk is a theoretical possibility in patients with PNH treated with complement inhibitors, based on the mode of action and nature of PNH. Haemolytic events are of noteworthy concern in patients with PNH who are receiving treatment with complement inhibitors which decrease both intravascular haemolysis (IVH) and extravascular haemolysis (EVH), owing to the potential for increased RBC clone size (Peffault de Latour et al 2022) (Risitano 2021) and subsequent serious haemolysis. Haemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed (Aspaveli SmPC). No adverse events of serious haemolysis following discontinuation of iptacopan were observed in the PNH clinical studies.
Risk factors and risk groups	Patients with PNH treated with complement inhibitors which decrease both IVH and EVH are at increased risk of serious haemolysis if treatment is discontinued, temporarily or permanently, due to increased PNH RBC clone size. In particular, patients who have not been established on an effective alternative therapy at the time of discontinuation are at higher risk for intravascular haemolysis (IVH) after drug discontinuation.
Risk minimization measures	**Routine risk communication** Risk addressed in SmPC Sections: - Posology and administration (Section 4.2) - Warning and Precautions (Section 4.4) Risk addressed in PL - Section 3 SmPC section 4.2 where description of the risk, along with treatment guidance is provided. - SmPC section 4.4 where monitoring of PNH manifestations after discontinuation is discussed. Calendarized packaging to aid in patient adherence to the dosing schedule. Legal status: Prescription only medicine **Additional risk minimization measures:** • Healthcare professional guide • Patient/caregiver guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CLNP023C12001B CLNP023C12003, PASS in iptacopan-treated patients using registry data See section II.C of this summary for an overview of the post-authorization development plan.

Table 4 – Important potential risk: Malignancies

Evidence for linking the risk to the medicine	Previous experience with other complement inhibitors (Ultomiris EPAR assessment report, Aspaveli EPAR Assessment report), suggests a possible class effect for these drugs. However, there is inconclusive literature evidence, with publications both suggesting tumor promotion and tumor inhibition by complement components (Revel et al 2020). Malignancies were observed in some patients with PNH treated with

	iptacopan 200 mg bid, however, most of these had relevant confounding conditions at study entry. Comprehensive preclinical carcinogenicity studies on iptacopan were negative.
Risk factors and risk groups	There is some evidence suggesting that patients with PNH may be more prone to develop tumors, with a prevalence of malignancies (other than MDS/AML) ranging from 2.2% - 14.2% (Yu et al 2016, Muñoz-Linares et al 2014). As per general (non-treated) patient population, older patients or patients with pre-cancerous conditions are risk groups.
Risk minimization measures	**Routine risk communication** Legal status: Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CLNP023C12001B CLNP023C12003, PASS in iptacopan-treated patients using registry data See section II.C of this summary for an overview of the post-authorization development plan.

Table 5 – Important missing information: Use in pregnant patients

Risk minimization measures	**Routine risk communication** Missing information addressed in SmPC sections - Fertility, pregnancy and lactation (Section 4.6) - Preclinical safety data (Section 5.3) Missing information addressed in PL - Section 2 Preclinical data and risks of pregnancy in PNH patients described. Lack of data on iptacopan in pregnancy and need for a risk-benefit assessment stated. Legal status: Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** CLNP023C12003, PASS in iptacopan-treated patients using registry data See section II.C of this summary for an overview of the post-authorization development plan.

Table 6 – Important missing information: Long-term safety (>2 years)

Risk minimization measures	**Routine risk communication:** Legal status: Prescription only medicine **Additional risk minimization measures:** None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CLNP023C12001B CLNP023C12003, PASS in iptacopan-treated patients using registry data See section II.C of this summary for an overview of the post-authorization development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of FABHALTA.

II.C.2 Other studies in post-authorization development plan

Table 7 – Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CLNP023C12001B Long-term safety and tolerability of iptacopan in patients with Paroxysmal Nocturnal Hemoglobinuria.	The purpose of this study is to evaluate the long-term safety, tolerability and efficacy of iptacopan in patients with PNH and to provide continued access to patients who have completed the treatment extension period (without tapering down) of the Phase II and Phase III trials and derived benefit from iptacopan treatment. To collect further data to help further characterize and/or closely monitor each of the respective safety concerns: • Infections caused by encapsulated bacteria • Serious haemolysis following discontinuation of iptacopan • Malignancies • Long-term safety (>2 years)
CLNP023C12003 PASS in iptacopan-treated patients using registry data	The purpose of this study is to characterize the identified and potential risks of iptacopan in the real-world clinical practice. Further study objectives are to provide additional data for the missing information (use in pregnancy and long-term safety) and to evaluate effectiveness of additional risk minimization measures (aRMMs) related to the required and recommended vaccinations in the iptacopan-treated PNH population. This study will use data collected through the International PNH Interest Group (IPIG) registry. The aim of the IPIG PNH registry is to develop an international database to prospectively collect observational data on patients with PNH (regardless of treatment received) covering clinical outcomes, patient reported outcomes, and health-resource utilization on all enrolled patients, as well as long term safety data. According to the IPIG PNH Registry protocol, Novartis will only have access to the data from PNH patients treated with iptacopan. The iptacopan PASS (a secondary analysis of the data collected in the registry) will thus be a single-arm study with no internal comparator.