SWISS SUMMARY OF THE RISK MANAGEMENT PLAN

for

Aspaveli

Active Substance: Pegcetacoplan

Version 1.0, 16 May 2023
Based on Version 1.0 of the EU RMP, 11 October 2021

Marketing Authorisation Holder: Swedish Orphan Biovitrum AG

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 Aspaveli 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 Aspaveli in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Swedish Orphan Biovitrum AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Aspaveli.

SUMMARY OF RISK MANAGEMENT PLAN FOR ASPAVELI

I THE MEDICINE AND WHAT IT IS USED FOR

Aspaveli is authorised for PNH (see SmPC for the full indication). It contains pegcetacoplan as the active substance, and it is given by subcutaneous infusion.

Further information about the evaluation of Aspaveli's benefits can be found in Aspaveli's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/aspaveli

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

Measures to minimise 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; and
- The medicine's legal status—the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

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

In the case of Aspaveli, these measures are supplemented with **additional risk minimisation measures** mentioned under relevant important risks and are listed below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report 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 Aspaveli is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Aspaveli are risks that need risk management activities to further investigate or minimise the risk so that the medicinal product can be safely administered. 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 Aspaveli. Potential risks are concerns for which an association with the use of this medicine is possible according to 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: Lists of Important Risks and Missing Information

List of important risks and missing information	
Important identified risks	None
Important potential risks	1. Serious infections 2. Serious hypersensitivity reactions 3. Intravascular haemolysis after drug discontinuation 4. Immunogenicity 5. Malignancies and haematologic abnormalities 6. Potential long-term effects of PEG accumulation
Missing information	1. Use in patients with bone marrow failure 2. Use in pregnant women 3. Long-term safety (>1 year)

Abbreviations: PEG = polyethylene glycol

II.B Summary of Important Risks

Important potential risk 1: Serious infections	
Evidence for linking the risk to the medicine	Inhibition of components of the complement system, including C3, might decrease innate immunity to encapsulated bacteria. This potentially increases the risk of serious infections from these bacteria in patients treated with pegcetacoplan. Studies have identified increased susceptibility to infection caused by encapsulated organisms as a key clinical consequence of congenital complement deficiency. Specifically, deficiency of C3 and its regulators (factor H and factor I) has been associated with severe recurrent bacterial infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* There have been no reports of serious infections with documented encapsulated bacteria attributable to pegcetacoplan through 334.5 person-years of systemic pegcetacoplan exposure. Therefore, the available safety data from the PNH patient studies do not make serious infections an identified risk at the present time.
Risk factors and risk groups	1. Unvaccinated patients or patients who do not maintain sufficient antibodies to the vaccines given before or during treatment might have a higher risk of infection due to encapsulated bacteria. 2. Patients with PNH-associated bone marrow failure (including aplastic anaemia PNH, myelodysplastic syndrome) have a higher risk of serious infection due to neutropenia 3. For patients who had solid organ (renal) or bone marrow transplants, receiving immunosuppressive treatment (eg, high-dose steroids, mycophenolate mofetil, ciclosporin, tacrolimus) is a risk factor 4. Individuals exposed to certain bacteria through work or travel might have a higher risk of infection. Groups at risk may include day-care workers, laboratory workers, military personnel, and other individuals with heightened levels of exposure to pathogenic bacteria.
Risk minimisation measures	Routine risk minimisation measures: • Summary of Product Characteristics (SmPC) Section 4.3, Section 4.4, and Section 4.8 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimisation measures: • Guide for healthcare professionals • Patient card • Patient/carer guide • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines) • System for controlled distribution
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study 307 • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk 2: Serious hypersensitivity reactions	
Evidence for linking the risk to the medicine	There was one report of serious hypersensitivity in Study 204. This moderate SAE of hypersensitivity was deemed related to pegcetacoplan by the investigator. The event, which occurred on Day 1 (ie, the subject's first day of dosing), led to the subject's discontinuation from the study. The subject was negative for anti–pegcetacoplan peptide antibody response on Day 1. One subject (Study APL2-204) had a mild TEAE of maculopapular rash deemed related to pegcetacoplan by the investigator. This event was temporally associated with positive serum anti-PEG antibodies but not anti–pegcetacoplan peptide antibodies. The rash subsequently resolved, and anti-PEG serology became negative despite uninterrupted treatment with pegcetacoplan. These 2 cases of hypersensitivity were treated and resolved. One subject in Study APL2-302 had an SAE of hypersensitivity pneumonitis. The absence of documented alternative explanations for the event of pneumonitis, as well as the subject's recovery after stopping pegcetacoplan, led the company to conclude that this event might have been treatment related. However, idiopathic interstitial lung disease is an alternative possibility. A review of nonclinical data from studies of pegcetacoplan did not reveal any specific risks for pulmonary hypersensitivity. In Study APL2-302, there was also one moderate SAE of allergy to immunoglobulin therapy, from which the subject recovered, and was considered to be unrelated to pegcetacoplan by the investigator. Injection site reactions were frequently reported, although none was severe or serious and treatment continued in all subjects without sequelae. The risk of serious hypersensitivity reactions is a theoretical potential risk because of the mechanism of action of pegcetacoplan and reports on potential for immunogenicity from PEG.
Risk factors and risk groups	Patients with a history of hypersensitivity to PEG are considered to have an increased risk of being hypersensitive to pegcetacoplan. In the pegcetacoplan clinical development programme, the immunogenicity potential of pegcetacoplan was assessed by evaluation of samples using validated assays for assessment of anti–pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. There was no apparent correlation of antibody development to altered pharmacokinetic profile. There has been no observed correlation of antidrug antibody development to clinical response or AEs in healthy subjects or subjects with PNH.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 and Section 4.4 • Package Leaflet Section 2 Additional risk minimisation measures: • Guide for healthcare professionals • Patient/carer guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study 307 • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk 3: Intravascular haemolysis after drug discontinuation (PNH)	
Evidence for linking the risk to the medicine	The PNH disease process and mechanism of control for it by complement inhibition is the source of this risk. Inhibition of complement C3 protects circulating red blood cells, produced by mutant stem-cell clones, from haemolysis. Discontinuation of treatment risks acute haemolytic crisis because of these red blood cells becoming vulnerable to destruction in patients with PNH. Hemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed.
Risk factors and risk groups	Patients with PNH who are being treated with a complement inhibitor and who have not been established on an effective alternative therapy at the time of discontinuation of a complement inhibitor are at higher risk for IVH after drug discontinuation.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 and Section 4.4 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimisation measures: • Guide for healthcare professionals • Patient/carer guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study 307 • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk 4: Immunogenicity	
Evidence for linking the risk to the medicine	Known potential of all medicinal products and on the class effect of all therapeutic proteins. No significant data have been identified for risk factors for immunogenicity in patients with PNH, neither within the conducted clinical trials for PNH nor identified in further publicly available articles or literature related to immunogenicity or antibodies to drug.
Risk factors and risk groups	In the pegcetacoplan clinical development programme, the immunogenicity potential of pegcetacoplan was assessed by evaluation of samples using validated assays for assessment of anti–pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. There was no apparent correlation of antibody development to altered pharmacokinetic profile. There has been no observed correlation of antidrug antibody development to clinical response or AEs in healthy subjects or subjects with PNH.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study 307 • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk 5: Malignancies and haematologic abnormalities	
Evidence for linking the risk to the medicine	Prior experience of PNH patients treated with C5 inhibitors and review of published data describing the risk of malignancies and haematologic abnormalities in patients with congenital complement deficiencies is the main reason for including this as an important potential risk.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: • None Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study 307 • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk 6: Potential long-term effects of PEG accumulation	
Evidence for linking the risk to the medicine	Preclinical findings from nonclinical studies of pegcetacoplan in rabbits and monkeys are the main reason for including this as an important potential risk. In general, PEG-associated cytoplasmic vacuolation has been considered an adaptive tissue response to long-chain PEG, which is widely considered a nonadverse finding, if not accompanied by evidence of cellular distortion, necrosis, degeneration, inflammation, or disturbed body function. The only exception is represented by the kidney, in which epithelial degeneration was observed. Short-term safety of PEG has been studied extensively without identification of toxicity beyond reports of renal tubular cell vacuolation and degeneration at very high dose levels. In some instances, vacuolation was significant, thus leading to tissue distortion, but yet without demonstrated adverse functional outcomes.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 and Section 5.3 Additional risk minimisation measures: • Guide for healthcare professionals
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study 307 • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Important missing information 1: Use in patients with bone marrow failure	
Risk minimisation measures	Routine risk minimisation measures: • None Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Important missing information 2: Use in pregnant women	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, Section 4.6 and Section 5.3 • Package Leaflet Section 2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Important missing information 3: Long-term safety (>1 year)	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, Section 4.4, Section 4.6, Section 4.8, Section 5.2 • Package Leaflet Section 4 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study 307 • PASS using registry data for pegcetacoplan See Section II.C of this summary for an overview of the postauthorisation development plan.

Abbreviations: AE = adverse event; PASS = postauthorisation safety study; PEG = polyethylene glycol; PNH = paroxysmal nocturnal haemoglobinuria; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of Aspaveli.

II.C.2 Other Studies in Post-Authorisation Development Plan

Post-Authorisation Safety Study (PASS) of Pegcetacoplan in Patients with PNH

This is a multinational, multicentre, observational PASS to assess the long-term safety of pegcetacoplan in a real-world setting. The purpose of this study is to gain more data on the long-term safety profile of pegcetacoplan and evaluate if the use of pegcetacoplan in adult patients with PNH increases the risk of certain adverse outcomes. The primary objective of this study is to evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan. Patients will be recruited through the IPIG registry. Patients with PNH confirmed by high-sensitivity flow cytometry and who initiate pegcetacoplan treatment for the first time will be included in the study at the time of treatment initiation. This study is observational and will not affect the patient and investigator relationship, nor influence the investigator's drug prescription or therapeutic management of the patient. The decision to treat patients with pegcetacoplan will be independent from the decision to enrol patients in the study.

Post-Authorization Safety Study (PASS) for Assessment of pregnancy outcomes in patients with PNH exposed to pegcetacoplan during pregnancy

This is a multinational, multicentre, observational PASS to collect and evaluate data on pregnancy outcomes and on the risk of adverse pregnancy outcomes in the offspring of women exposed to pegcetacoplan during pregnancy. The primary objective of this study is to evaluate the rate of foetal deaths/stillbirths among pregnancy outcomes in patients treated with pegcetacoplan. Patients will be recruited through the IPIG registry. This study is observational and will not affect the patient/investigator relationship, nor influence the investigator's drug prescription or therapeutic management of the patient. The decision to treat patients with pegcetacoplan will be independent from the decision to enrol patients in the study.

An Open-Label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegcetacoplan in the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)

An open-label, nonrandomised, multicentre extension Phase 3 long-term extension study for patients with PNH (Study 307). This extension study protocol was developed to continue evaluation of the long-term safety and efficacy of pegcetacoplan in subjects with PNH. The objectives of this study are to establish the long-term safety of pegcetacoplan in subjects with PNH and to establish the long-term efficacy of pegcetacoplan in subjects with PNH. Subjects who have completed other pegcetacoplan PNH clinical trials are eligible to participate in this trial.