Summary of the Risk Management Plan (RMP)

for

ASPAVELI®

(pegcetacoplan)

Based on EU RMP version 3.0

Marketing Authorisation Holder: Swedish Orphan Biovitrum AG

Document dated 08 January 2025

Disclaimer:

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 (pegcetacoplan)

This is a summary of the risk management plan (RMP) for Aspaveli. The RMP details important risks of Aspaveli, how these risks can be minimized, and how more information will be obtained about Aspaveli's risks and uncertainties (missing information).

Aspaveli's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Aspaveli should be used.

This summary of the RMP for Aspaveli should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of Aspaveli's RMP.

I. The medicine and what it is used for

Aspaveli is authorized 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.

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

Important risks of Aspaveli, together with measures to minimize such risks and the proposed studies for learning more about Aspaveli'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 authorized 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 (e.g., with or without prescription) can help to minimize its risks.

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, 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 minimize 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).

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

Abbreviation: BMF, Bone marrow failure; IVH, Intravascular hemolysis; 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 meningococcal infections through 818.36 personyears of systemic pegcetacoplan exposure in ongoing and completed clinical trials and 626.58 person-years of systemic pegcetacoplan exposure in the post marketing setting.

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 BMF (including aplastic anemia PNH and myelodysplastic syndrome) have a higher risk of serious infection due to neutropenia. 3. For patients who had solid organ (renal) or BMTx, receiving immunosuppressive treatment (e.g., high-dose steroids, mycophenolate mofetil, ciclosporin, and 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 minimization measures	Routine risk minimization measures: • SmPC Section 4.3, Section 4.4, and Section 4.8 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimization 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 APL2-307 • PASS Sobi.PEGCET-301 See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: BMF, Bone marrow failure; BMTx, Bone marrow transplantation; PASS, Post authorization safety study; PNH, Paroxysmal nocturnal hemoglobinuria; SmPC, Summary of product characteristics.

Important potential risk 2: Serious hypersensitivity reactions	
Evidence for linking the risk to the medicine	There was 1 report of serious hypersensitivity in Study APL2-CP-PNH-204. This moderate SAE of hypersensitivity was deemed by the investigator to be related to pegcetacoplan. The event, which occurred on Day 1 (i.e., the subject's 1st 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. Another subject in Study APL2-204 had a mild TEAE of maculopapular rash deemed by the investigator to be related to pegcetacoplan. 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. In Study APL2-302, 18 subjects treated with pegcetacoplan experienced a hypersensitivity event. Most were mild or moderate in intensity. Erythema, rhinitis allergic, and acute respiratory failure were the most common TEAEs. 5 subjects experienced hypersensitivity events that were considered related to pegcetacoplan (acute respiratory failure, erythema, hypersensitivity pneumonia, mechanical urticaria, and pruritus). 3 subjects had severe hypersensitivity events, including 1 subject who had an SAE of hypersensitivity pneumonitis that led to study discontinuation. In Study APL2-308, 12 subjects treated with pegcetacoplan experienced a hypersensitivity event. All were mild or moderate in intensity. Erythema, rash, and rash maculopapular were the most common TEAEs. 3 subjects experienced hypersensitivity events that were considered related to pegcetacoplan (rash [2 events] and rash maculopapular). In Study APL2-302, ISRs were frequently reported, although none was severe or serious, and treatment continued in all subjects without sequelae. In Study APL2-308, 16 subjects in the overall pegcetacoplan group had at least 1 ISR. All ISRs were mild in severity; there were no moderate or severe ISRs. Erythema was the most commonly reported ISR. 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. In the post marketing setting, very limited information was provided for 2 cases of anaphylactic reaction in subject on pegcetacoplan; however, in both cases, pegcetacoplan treatment was continued, and the events resolved. In addition, 1 case of supposed anaphylactic shock has been reported, which was considered by the company to be related to pegcetacoplan given the plausible temporal relationship and lack of alternate etiologies.
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 program, 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 an altered PK profile. There has been no observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 and Section 4.4 • Package Leaflet Section 2 Additional risk minimization measures: • Guide for healthcare professionals

	• Patient/carer guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS Sobi.PEGCET-301 See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: ADA, Antidrug antibodies; ISR, Injection site reaction; PASS, Post authorization safety study; PEG, Polyethylene glycol; PK, pharmacokinetic; PNH, Paroxysmal nocturnal hemoglobinuria; SAE, Serious adverse event; SmPC, Summary of product characteristics; TEAE, Treatment-emergent adverse event.

Important potential risk 3: IVH after drug discontinuation	
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 RBCs, produced by mutant stem cell clones, from hemolysis. Discontinuation of treatment risks acute hemolytic crisis because of these RBCs becoming vulnerable to destruction in patients with PNH. Hemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed. In Study APL2-204, 1 subject had pegcetacoplan administration withheld for 8 days because of a herpes zoster infection. The subject was instructed by the investigator to resume administration immediately and received pegcetacoplan on the next 2 days. On the following day, the subject withheld pegcetacoplan dosing because of abdominal discomfort and was subsequently diagnosed with severe hemolysis. The gap in this subject's pegcetacoplan dosing was associated with the onset of hemolysis. In Study APL2 CP0514, pegcetacoplan treatment was temporarily ceased for 1 subject following an SAE of alanine aminotransferase increased. 20 days later, the subject had an SAE of anemia that was attributed to rebound hemolysis following cessation of pegcetacoplan treatment. In the RCP of Study APL2-302, some hemolytic events occurred in the eculizumab group for which the investigator assessed the causal relationship to the study drug as possibly or definitely related to pegcetacoplan. It should be noted that subjects were not receiving pegcetacoplan during the RCP, but the investigator attributed the event to the discontinuation of pegcetacoplan after the run-in period. No events of hemolysis occurred because of missed or delayed pegcetacoplan or eculizumab doses. In Study APL2-302, 22 subjects treated with pegcetacoplan experienced a hemolytic event. Most events were moderate or severe in intensity. 8 subjects experienced serious hemolytic events. Hemolysis was the most common TEAE occurring in 19 subjects (23.8 %). 3 subjects experienced hemolysis that were considered related to pegcetacoplan. As a result of the hemolytic events, the dose of pegcetacoplan was increased in 10 subjects, and the study drug was withdrawn in 5 subjects. In the

	randomized controlled period of the study, hemolysis TEAE occurred less frequently in the pegcetacoplan group than in the eculizumab group. This suggests that no additional risk for hemolysis is associated with pegcetacoplan treatment. In Study APL2-308, 2 subjects treated with pegcetacoplan experienced a hemolytic event. 1 event was moderate and 1 event was severe in intensity. 1 additional subject in the standard of care to pegcetacoplan group experienced a moderate event of hemolysis. In all 3 instances, the events resulted in a dose increase. In the post marketing setting, there has been one report of hemolysis that occurred after pegcetacoplan discontinuation. Symptoms resolved in 1 to 2 days after treatment with pegcetacoplan was resumed.
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 minimization measures	Routine risk minimization measures: • SmPC Section 4.2 and Section 4.4 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimization 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 APL2-307 • PASS Sobi.PEGCET-301 See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: IVH, Intravascular hemolysis; PNH, Paroxysmal nocturnal hemoglobinuria; RBC, Red blood cell; SmPC, Summary of product characteristics; TEAE, Treatment-emergent adverse event.

Important potential risk 4: Immunogenicity	
Evidence for linking the risk to the medicine	Immunogenicity is a known potential of all medicinal products and is a class effect of all therapeutic peptides and 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 program, 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 an altered PK profile. There has been no observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: AE, Adverse event; ADA, Antidrug antibodies; PASS, Post authorization safety study; PEG, Polyethylene glycol; PK, pharmacokinetic; PNH, Paroxysmal nocturnal hemoglobinuria; SmPC, Summary of product characteristics.

Important potential risk 5: Malignancies and hematologic 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 hematologic 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 minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: PASS, Post authorization safety study; PNH, Paroxysmal nocturnal hemoglobinuria.

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 reasons 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 non-adverse 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 minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and Section 5.3 Additional risk minimization measures: • Guide for healthcare professionals
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: PASS, Post authorization safety study; PEG, Polyethylene glycol; SmPC, Summary of product characteristics.

Important missing information 1: Use in patients with BMF	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: BMF, Bone marrow failure; PASS, Post authorization safety study.

Important missing information 2: Use in pregnant women	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, Section 4.6 and Section 5.3 • Package Leaflet Section 2 Additional risk minimization measures: • None

Abbreviations: SmPC, Summary of product characteristics.

Important missing information 3: Long-term safety (>1 year)

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.6, Section 4.8, Section 5.2 • Package Leaflet Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: PASS, Post authorization safety study; SmPC, Summary of product characteristics.

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 Aspaveli.

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

PASS of pegcetacoplan in patients with PNH (Study Sobi.PEGCET-301)

This is a multinational, multicenter, 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. Patient data in this study will be extracted from the database of the ongoing observational study Sobi.PEGCET-304 which is collecting all AEs. 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 enroll 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 PNH (Study APL2-307)

An open-label, nonrandomized, multicenter extension phase 3 long-term extension study for patients with PNH. 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.