Swiss Summary of the Risk Management Plan (RMP) for Rurioctocog alfa pegol (ADYNOVI)

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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 risk as well as to prevent or minimize them.

The RMP summary of ADYNOVI 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 ADYNOVI in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of ADYNOVI.

Summary of risk management plan for ADYNOVI (Rurioctocog alfa pegol)

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

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

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

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

I. The medicine and what it is used for

ADYNOVI is authorised for treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency) (see SmPC for the full indication). It contains rurioctocog alfa pegol as the active substance and after reconstitution, the solution is administered by injection via intravenous route.

Further information about the evaluation of ADYNOVI's benefits can be found in ADYNOVI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.: https://www.ema.europa.eu/en/medicines/human/EPAR/adynovi

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ADYNOVI, together with measures to minimise such risks and the proposed studies for learning more about ADYNOVI '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;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

II.A List of important risks and missing information

Important risks of ADYNOVI are risks that need special 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 ADYNOVI. 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);

List of important risks and missing information	
Important identified risks	• Inhibitor formation • Hypersensitivity reactions
Important potential risks	• Thromboembolic events • Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs (including in case of off-label use in children below the age of 12 years) • Anti-PEG FVIII antibodies • Overdosing (thrombosis) when switching to ADYNOVI from another FVIII product or underdosing (lack of efficacy/bleeding) when switching from ADYNOVI to another FVIII product
Missing information	• Use in patients ≥ 65 years of age • Use in PUPs • Use of ADYNOVI for ITI • Use during pregnancy and lactation

II.B Summary of important risks and missing information

Important Identified Risk: Inhibitor formation	
Evidence for linking the risk to the medicine	The formation of neutralizing antibodies (inhibitors) against FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG directed against the FVIII procoagulant activity, which are quantified in Bethesda units (BU) per mL of plasma using the modified Bethesda (Nijmegen) assay. In patients who develop inhibitors to FVIII, the condition may manifest itself as an insufficient clinical response.
Risk factors and risk groups	Risk groups include populations with a medical history of FVIII inhibitors, certain gene mutations (e.g., null, large deletion), ethnicity, family history, and age at first exposure [32]. In addition, there may be an increased risk of inhibitor development in PUPs with a positive family history of inhibitor development. Studies report a 48% risk of inhibitor development in patients with first-degree family history, as compared to those without this history risk who have a 3x lower risk of development [11,32,33].

	The risk of developing inhibitors is correlated to the age at first exposure to FVIII therapy and the extent of exposure to FVIII, the risk being highest within the initial EDs [32]. Approximately half of the new inhibitors (49%) presented before the patient was 5 years of age [34]. PUPs may have undiagnosed high-risk gene mutations which may pre-dispose the patient to inhibitor formation. The incidence of inhibitors initially declines with increasing age before rising to a second peak of 10.49 new inhibitors per 1000 PY at risk in patients ≥60 years of age [34]. Response to treatment may depend on patient-specific dosing requirements due to differences of PK parameters. Treatment related risk factors for inhibitor development include number of EDs (the risk being highest during early EDs), intense exposure (risk increased with 5 or more EDs at first treatment), and surgery (risk increased if surgery combined with intensive first exposure (>4 EDs) [32].
Risk minimization measures	**Routine risk minimisation measures:** Sections 4.4, 4.8 in the EU SmPC Sections 2 and 4 of the PL **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Paediatric PUP study 261203 • PASS TAK-660-403

Important Identified Risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Among patients treated with FVIII concentrates (e.g., ADVATE), serious hypersensitivity reactions have been occasionally observed in clinical trials. Post-Marketing case reports also support the classification.
Risk factors and risk groups	Patients with previous history of hypersensitivity and allergic reactions to the active substance or any of the excipients may be at increased risk. Medical history of hypersensitivity and allergic reactions to the active substance, to mouse or hamster proteins, or any of the excipients.
Risk minimization measures	**Routine risk minimisation measures:** Sections 4.3, 4.4, and 4.8 in the EU SmPC Sections 2 and 4 of the PL **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional	**Additional pharmacovigilance activities:**

pharmacovigilance activities	• Paediatric PUP study 261203 • PASS TAK-660-403

Important Potential Risk: Thromboembolic events	
Evidence for linking the risk to the medicine	High and sustained levels of FVIII activity have been statistically associated with arterial or venous thrombosis in individuals with underlying risk factors for thrombosis [44]. There is a paucity of evidence to support such a risk in the context of transiently high levels of FVIII activity, or in the target patient population.
Risk factors and risk groups	Patients with liver disease, peri- and post-operative patients, newborn infants, or other patients at risk for thromboembolic events or DIC
Risk minimization measures	**Routine risk minimisation measures:** None proposed **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS TAK-660-403

Important Potential Risk: Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs (including in case of off-label use in children below the age of 12 years)	
Evidence for linking the risk to the medicine	Preclinical safety data Section 5.3 of the EU SmPC
Risk factors and risk groups	All patient populations are potentially exposed to PEG by way of consumer products and in parenteral and oral pharmaceuticals
Risk minimization measures	**Routine risk minimisation measures:** Section 5.3 in the EU SmPC **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS TAK-660-403

Important Potential Risk: Anti-PEG FVIII antibodies	
Evidence for linking the risk to the medicine	One subject experienced a mild systemic hypersensitivity reaction that was in temporal association with IgG/IgM PEG- FVIII and IgG/IgM PEG antibodies whereas the subject tested negative for IgE antibodies

	against FVIII and PEG-FVIII. Based on available data, a causal relationship can neither be confirmed nor excluded.
Risk factors and risk groups	Healthy individuals and PWH are routinely exposed to substantial amounts of PEG (lotions, creams, laxatives and biotherapeutics)
Risk minimization measures	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Paediatric PUP study 261203 • PASS TAK-660-403

Important Potential Risk: Overdosing (thrombosis) when switching to ADYNOVI from another FVIII product or underdosing (lack of efficacy/bleeding) when switching from ADYNOVI to another FVIII product	
Evidence for linking the risk to the medicine	Literature, Global Safety Database
Risk factors and risk groups	Patients switching to ADYNOVATE from another FVIII product or patients switching from ADYNOVATE to another product.
Risk minimization measures	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS TAK-660-403

Missing Information: Use in patients > 65 years of age	
Risk minimization measures	**Routine risk minimisation measures:** Section 5.1 in the EU SmPC **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS TAK-660-403

Missing Information: Use in PUPs	
Risk minimization measures	**Routine risk minimisation measures:** Section 4.2 in the EU SmPC **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Paediatric PUP study 261203

Missing Information: Use of ADYNOVI for ITI	
Risk minimization measures	**Routine risk minimisation measures:** Sections 4.4 in the EU SmPC **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Paediatric PUP study 261203

Missing Information: Use during pregnancy and lactation	
Risk minimization measures	**Routine risk minimisation measures:** Section 4.4 in the EU SmPC Section 2 of the PL **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C. Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

- PASS TAK-660-403

Purpose of the study: To evaluate the long-term safety of ADYNOVI/ADYNOVATE prophylaxis in patients with haemophilia A when used under standard clinical practice in the real-world setting.

Primary objective: To assess the long-term safety of prophylaxis with ADYNOVI/ADYNOVATE in patients with haemophilia A in the real-world clinical setting through the collection and analysis of adverse events (AEs) of special interest (long-term potential effects of PEG accumulation [such as renal, hepatic and

neurological events], thromboembolic events, hypersensitivity reactions, lack of efficacy and inhibitor development), AEs, serious adverse events (SAEs), and adverse drug reactions (ADRs).

Secondary objective: To monitor the clinical effects of long-term exposure of prophylaxis with ADYNOVI/ADYNOVATE in patients with haemophilia A, including assessments of kidney and liver function parameters, neurological function, and patients' PEG plasma levels.

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

- Paediatric PUP study 261203

Purpose of the study: The purpose of the study is to investigate the safety, immunogenicity and haemostatic efficacy of PEGylated recombinant FVIII (BAX 855) in PUPs <6 years of age with severe haemophilia A (baseline FVIII level < 1%) and < 3 EDs to ADVATE, BAX 855 or FFP.

The primary objective of the study is to determine the safety including immunogenicity of BAX 855 based on the incidence of inhibitor development to FVIII (≥ 0.6 BU/mL using the Nijmegen modification of the Bethesda assay).

The secondary objective is to evaluate efficacy and safety of ITI with BAX855 and to determine the rate of success, partial success and failure of ITI with BAX 855