Summary of Risk Management Plan

ADYNOVI

rurioctocog alfa pegol

Version 3.1

Takeda Pharma AG

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Summary of the risk management plan (RMP) for ADYNOVI (rurioctocog alfa pegol)

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 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.swissmedic.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.

Overview of Disease Epidemiology

Haemophilia A is a rare bleeding disorder that is primarily found in males, in which the blood does not clot normally. Individuals with haemophilia A have little or no clotting factor VIII. This clotting factor VIII is an important protein needed for normal blood clotting.

Globally, haemophilia A occurs in 20 out every 100,000 male births. Of the patients with haemophilia A, approximately 45% to 60% are found worldwide to have severe disease. The World Federation of Haemophilia 2017 Annual Global Survey Report published that Switzerland had 418 patients with haemophilia A or B identified in 2017.

Although patients with mild haemophilia A have acute bleeding episodes usually after trauma or surgery, those with severe haemophilia A suffer frequently with unexpected bleeding particularly in joints and muscles. Such uncontrolled bleeding episodes can lead to organ damage and joint destruction. Yet, due to improvements in haemophilia care there is a growing number of older people with haemophilia A. However, those who do not receive treatment may suffer with uncontrolled bleeds and increased disease burden due to chronic joint disease, severe disability, and increased risk of death.

Summary of Treatment Benefits

The main treatment for haemophilia is called replacement therapy. Concentrates of clotting factor VIII (for haemophilia A) are given to help replace the clotting factor that is missing or low.

Some clotting factors are made from human blood which have the remote risk of acquiring an infectious disease (for example, hepatitis). ADYNOVI is produced from ADVATE and does

not contain material from human blood. The benefit of using ADYNOVI is a minimized risk of getting an infectious disease.

Like ADVATE, ADYNOVI replaces the clotting factor that is missing or low. An added benefit of ADYNOVI is that it is long-acting, thereby lowering the number of infusions needed per week.

Replacement therapy can occur on a regular basis to prevent bleeding. This is called preventive or prophylactic therapy. Replacement therapy may only be needed to stop bleeding when it occurs. This use of the treatment, on an as-needed basis, is called on-demand therapy. However, there is a risk that bleeding will cause damage before the patient receives the on-demand therapy.

Unknowns Relating to Treatment Benefits

Clinical studies did not include patients aged 65 years and older. It is not known whether elderly patients respond differently to ADYNOVI than other patients. The safety, efficacy, and PK profile were comparable between children <12 years old and 12 to <18 years old. Previously untreated patients were not included thus far in clinical studies with ADYNOVI.

Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Antibodies against factor VIII which may reduce the effectiveness of ADYNOVI to prevent or control bleeding (Inhibitor formation)	Talk to your doctor immediately if your bleeding does not stop as expected. Your doctor will do a blood test to check if you have developed an activity-neutralizing antibody (inhibitor) against ADYNOVI. The risk for developing an inhibitor is highest in patients who have not been treated with a factor VIII replacement medicine before or in the early phases of treatment, i.e., for small children.	Not applicable.
Allergic reactions to the main ingredient or any of the other components of the medicine (Hypersensitivity reactions)	Potentially life-threatening reactions (anaphylaxis) and other allergic reactions (hypersensitivity) can occur. Stop your infusion and contact your doctor immediately or seek emergency medical care if you experience early signs of hypersensitivity/allergic reactions like hives, rash, tightness of the chest, wheezing, low blood pressure or anaphylaxis (severe allergic reaction that can cause difficulty in swallowing and/or breathing, red or swollen face and/or	Not applicable.

Important Identified Risks

Risk	What is Known	Preventability
	hands). Your doctor may need to treat you promptly for these reactions. ADYNOVI should not be used if you are allergic (hypersensitive) to the product or any of the other ingredients of this medicine or if you are allergic to mouse or hamster protein.	

Important Potential Risks

Risk	What is Known
Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs	The long-term effect of PEG exposure in humans is not known. Should the patient develop any sign / symptoms of renal, hepatic or neurological abnormalities, the patient should consult the doctor.

Missing Information

Risk	What is Known
No clinical data on use in geriatric patients ≥ 65 years of age	Clinical studies with ADYNOVI did not include patients 65 years and older. It is not known whether patients 65 years and older would respond differently than younger patients.
No clinical data on use in previously untreated patients	Clinical studies with ADYNOVI did not include previously untreated patients. Previously untreated patients would most likely be exposed for the first time in childhood. The risk for developing an inhibitors is highest in patients who have not been treated with a factor VIII replacement medicine before or in the early phases of treatment, i.e., for small children.
Use of ADYNOVI for Immune Tolerance Induction (ITI)	No clinical data for use of ADYNOVI for ITI therapy is available.
Use during pregnancy and lactation	Pregnant and breast-feeding women were not included in clinical studies with ADYNOVI. No clinical studies have been done in women, including those who may be pregnant and/or breast-feeding. Therefore, it is unknown whether it is safe for these women to take ADYNOVI.

Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

Planned Post-Authorization 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%).

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).

Studies which are a Condition of the Marketing Authorization

There are no studies that are conditions of the marketing authorization.

Summary of Changes to the Risk Management Plan Over Time

This is Summary of Swiss RMP for ADYNOVI, version 3.1.