EU RISK MANAGEMENT PLAN (RMP)

for

RURIOCTOCOG ALFA PEGOL (ADYNOVI)

RMP Version number: 5.0

Date: 28-March-2025

[redacted]

[redacted]

EU Risk Management Plan for RURIOCTOCOG ALFA PEGOL (ADYNOVI)

RMP version to be assessed as part of this application:

RMP Version number: 5.0

Data lock point for this RMP: 12-November-2024

Date of final sign-off: 28-March-2025

Rationale for submitting an updated RMP: The RMP has been revised to include updates based on completion of Paediatric previously untreated patients (PUP) study 261203

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable
• **Module SII Non-clinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Updated as of DLP 12-November-2024.
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Updated as of DLP 12-November-2024.
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	• The characterisation of risks counts have been updated as of DLP 12-November-2024. • Missing information "Use in PUPs" and "Use of Adynovi for ITI" are removed. Provided justification for the removal of these safety concerns.
• **Module SVIII Summary of the safety concerns**	Missing information "Use in PUPs" and "Use of Adynovi for ITI" are removed.
Part III Pharmacovigilance plan	The section has been revised to remove study 261203 and hypersensitivity questionnaire.
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	• V.1 Routine risk minimisation measures updated with removal of missing information "Use in PUPs" and "Use of Adynovi for ITI" • V.3 Summary of Risk Minimisation Measures updated with removal of hypersensitivity

RMP Module:	Significant Changes:
	questionnaire under routine PV activities and study 261203 under additional PV activities
Part VI Summary of the risk management plan	Updated to be consistent with Part III and Part V updates
Part VII Annexes	Annex 2: Study 261203 was removed from planned and ongoing studies and was added under the completed studies. Annex 3: Updated with removal of Study 261203 under approved protocols Annex 4: Hypersensitivity questionnaire was removed Annex 8: Updated to reflect the changes made from version 4.0 to 5.0

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 4.0

Approved with procedure: EMEA/H/C/004195/IB/0037

Date of approval (opinion date): 01-June-2023

Approver credentials:

QPPV: Jean-Marie Heim, MD

Please note that signature may also be performed by Deputy EU QPPV [redacted] *on behalf of the EU QPPV (i.e., 'per procurationem').*

Approver signature: Signatures are available on file.

[redacted]

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[redacted]

List of Abbreviations

Abbreviation	Definition/Description
aPTT	Activated Partial Thromboplastin Time
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ATC code	Anatomical Therapeutic Chemical classification system
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CNS	Central Nervous System
CSR	Clinical Study Report
DLP	Data Lock Point
DNA	Deoxyribo nucleic acid
EC	European Commission
ED	Exposure Days
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FDP	Final Drug Product
GSDB	Global Safety Database
GVP	Good Pharmacovigilance Practice
HGB	Hemoglobin

[redacted]

Abbreviation	Definition/Description
HCV	Hepatitis C Virus
HCT	Hematocrit
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
INN	International Non-proprietary Names
ITI	Immune Tolerance Induction
IU	International Units
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDMs	Monocyte-derived Macrophages
NOAEL	No observed adverse effect level
PASS	Post-Authorisation Safety Study
PEG	Polyethylene glycol
PI	Product Information
PK	Pharmacokinetic
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PUP	Previously Untreated Patients
PY	Patient years
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
RBC	Red Blood Cells
RMP	Risk Management Plan

Abbreviation	Definition/Description
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
UK	United Kingdom
US	United States

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	PEGylated recombinant human factor VIII (rurioctocog alfa pegol)
Pharmacotherapeutic group(s) (ATC Code)	Coagulation factor VIII: B02BD02
Marketing Authorisation Holder	Baxalta Innovations GmbH (a wholly owned subsidiary of Takeda Pharmaceutical Company Limited).
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ADYNOVI*
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class ADYNOVI, rurioctocog alfa pegol, is a PEGylated full- length recombinant human factor VIII with an extended half-life. Rurioctocog alfa pegol is a covalent conjugate of ADVATE [octocog alfa] consisting of 2,332 amino acids with polyethylene glycol (PEG) reagent (MW 20 kDa). The therapeutic activity of ADYNOVI is derived from ADVATE, which is produced by recombinant DNA technology from a Chinese hamster ovary cell line. The ADVATE molecule is then covalently conjugated with the PEG reagent, which targets lysine residues. The PEG moiety is conjugated to the ADVATE molecule to increase the plasma half-life through the reduction of the LRP-1 receptor-mediated clearance of the factor VIII molecule.
	Summary of mode of action The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.
	Important information about its composition ADYNOVI for intravenous injection and is provided in single-dose vials, which contain nominally 250, 500, 1000, 2000 and 3000 International Units (IU) rurioctocog alfa pegol. The powder for injection is reconstituted with 2 mLor 5 mL sterile water for

<table>
<tr><td></td><td>injection. The potency (IU) is determined using the chromogenic assay. The specific activity of ADYNOVI is approximately 3800-6500 IU/mg protein.

When reconstituted with the appropriate volume of diluent, ADYNOVI contains the excipients: mannitol, trehalose dihydrate, histidine, glutathione, sodium chloride, calcium chloride dihydrate, tris (hydroxymethyl)aminomethane, polysorbate 80 and sterilized water for injections.</td></tr>
<tr><td>Hyperlink to the Product Information (PI)</td><td>Approved ADYNOVI SmPC</td></tr>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current:

Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).</td></tr>
<tr><td>Proposed:

Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current :

The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

On demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The required dose is determined using the following formula:

Required international units (IU) = body weight (kg) x desired factor VIII rise (%) x 0.5

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period.

The following Table 1 can be used to guide dosing in bleeding episodes and surgery:

<table>
<tr><td colspan="3">Table 1 Guide for dosing in bleeding episodes and surgery</td></tr>
<tr><td>Degree of haemorrhage/type of surgical procedure</td><td>Factor VIII level required (% or IU/dL)</td><td>Frequency of doses (hours)/duration of therapy (days)</td></tr>
<tr><td colspan="3">Haemorrhage</td></tr>
<tr><td>Early haemarthrosis,</td><td>20 – 40</td><td>Repeat injections</td></tr>
</table>
</td></tr>
</table>

[redacted]

muscle bleeding or oral bleeding.		every 12 to 24 hours. At least 1 day, until the bleeding episode, as indicated by pain, is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 – 60	Repeat injections every 12 to 24 hours for 3 – 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages.	60 – 100	Repeat injections every 8 to 24 hours until threat is resolved.
Surgery		
Minor Including tooth extraction.	30 – 60	Every 24 hours at least 1 day, until healing is achieved.
Major	80 – 100 (pre- and postoperative)	Repeat injections every 8 to 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

Prophylaxis

For long term prophylaxis, the recommended dose is 40 to 50 IU of ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Paediatric population

On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. The long-term safety of ADYNOVI in children below 12 years has not yet been established. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Proposed:

Not applicable

[redacted]

Pharmaceutical form(s) and strengths	Current (if applicable): ADYNOVI 250 IU / 5 mL powder and solvent for solution for injection ADYNOVI 500 IU / 5 mL powder and solvent for solution for injection ADYNOVI 1000 IU / 5 mL powder and solvent for solution for injection ADYNOVI 2000 IU / 5 mL powder and solvent for solution for injection ADYNOVI 250 IU / 2 mL powder and solvent for solution for injection ADYNOVI 500 IU / 2 mL powder and solvent for solution for injection ADYNOVI 1000 IU / 2 mL powder and solvent for solution for injection ADYNOVI 3000 IU / 5 mL powder and solvent for solution for injection
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

*The approved name for rurioctocog alfa pegol, antihemophilic factor [recombinant] PEGylated globally is ADYNOVATE and in EU it is ADYNOVI. This RMP includes safety information concerning both tradenames which are used interchangeably throughout the document.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Epidemiology for treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).	
Incidence:	According to worldwide data available for the congenital bleeding disorder, haemophilia A, the estimated incidence has been reported as approximately 20 cases per 100,000 male births and is expected to be found at similar rates globally among different populations[redacted]. This disease which accounts for nearly 9 out of 10 haemophilia cases is caused by a loss or deficient production of clotting factor VIII, thereby leaving individuals susceptible to prolonged bleeding[redacted]. In patients with haemophilia A, susceptibility to uncontrolled bleeding is influenced by disease severity defined by the baseline plasma factor levels of 5% to 40% (mild), 1% to 5% (moderate), or <1% (severe)[redacted]. Of the patients with haemophilia A, approximately 45% to 60% are reported to have severe disease [redacted]. Although patients with mild haemophilia have acute bleeding episodes usually after trauma or surgery, those with severe haemophilia suffer frequently with spontaneous haemorrhage, particularly in joints and muscles, which can lead to debilitating arthropathy[redacted].
Prevalence:	The prevalence of haemophilia A, varying from moderate to severe, is reported to range from 0.4 to 20.7 cases per 100,000 males in different regions of the world[redacted]. During the 1970s the prevalence in the United States (US) was estimated at 20 cases per 100,000 males, with a lower rate in the United Kingdom (UK) of 10 cases per 100,000 males. While the rates in the US have declined, other countries have reported an increase in prevalence similar to the UK with a steady rising trend in burden of disease over the last two decades[redacted]. Reported regional differences in prevalence may reflect a combination of factors including changes in reporting practices and differences in patient outcomes reported around the globe.
Demographics of the target population in the indication:	Haemophilia A is an X-linked chromosomal recessive disorder. Haemophilia A generally affects males on the maternal side. Haemophilia A is often diagnosed during childhood and may manifest as bruising, spontaneous bleeding (particularly in the joints, muscles, and soft tissues), and excessive bleeding from surgery or trauma. Disease severity is dictated by plasma FVIII levels with approximately 60% of patients having severe disease, defined by FVIII levels <1% of normal, and the remaining patients have moderate (FVIII levels 1-5%) or mild disease (FVIII levels >5-40%).

Epidemiology for treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).	
The main existing treatment options:	At present, FVIII replacement is the only symptomatic and preventative therapy available for the treatment of haemophilia A. Use of a FVIII product begins at the onset of symptoms in childhood and continues throughout the patient's life.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	Before the 1970s, life expectancy of individuals with haemophilia was very low (<30 years) in comparison to that of the general male population, with haemorrhage as the most common cause of death[redacted]. Following that time, a sharp mortality peak due to viral contamination during the 1980s and 1990s, led to AIDS accounting for 55% of all haemophilia deaths. While AIDS remains the most common cause of death in patients with severe haemophilia, along with cirrhosis from hepatitis, mortality among people with haemophilia has declined substantially. This decline was attributed to the availability of clotting factor replacement products, and improved and specialized management in haemophilia treatment centers [redacted]. Those infected with HIV are more likely to die of the virus rather than from haemophilia [redacted]. As a result of safer blood products and more effective treatments for HIV and Hepatitis C Virus (HCV) the life expectancy of those with haemophilia is progressively approaching that of the general population[redacted]. In a large observational study of haemophilia patients, HIV-negative men with severe haemophilia were found to have a median life expectancy of 63 years, and for HIV-negative men with mild or moderate haemophilia the median life expectancy is 75 years, compared with 78 years in the UK for the general male population [redacted]. Therefore, the ageing haemophilic population has developed medical and surgical conditions typically associated with ageing, such as cardiovascular disease and cancer, and these diseases are likely to be new causes of mortality for this population[redacted]. Due to advances in haemophilia care there is a growing number of older people with haemophilia; however, those who are unable to receive adequate treatment suffer from uncontrolled bleeds and increased morbidity due to chronic arthropathy, severe disability, and increased risk of death [redacted].
Important co-morbidities:	Co-morbidities of haemophilia A in the target population include cardiovascular disease, viral diseases (e.g., HIV, HBV, and HCV), and malignancies (especially in elderly haemophilia patients).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity:	
Single-dose toxicity	
No separate single-dose toxicity studies were performed. Single dose toxicity was assessed based on the data from the one dose-escalation study in cynomolgus monkeys. There were no signs of toxicity at any dose level, no mortalities or test item or reference item-related changes in the endpoints of the study except for slightly elevated levels of glutamate dehydrogenase and aspartate aminotransferase detected in single animals of the low, mid and high dose group of ADYNOVI which did not result in toxicologically relevant findings. Therefore, treatment with two different batches of ADYNOVI was well tolerated with a no observed adverse effect level (NOAEL) of 1500 IU FVIII/kg.	No toxicologically relevant findings. No signs of toxicity were observed at any dose level. Assessment of single dose toxicity in cynomolgus monkeys supports the conclusion that ADYNOVI is safe for human use.
Repeat-dose toxicity	
Repeat-dose toxicity studies were conducted in rats and cynomolgus monkeys. Rats were dosed intravenously with 350 or 700 IU FVIII/kg ADYNOVI (two lots) every other day over 29 days (15 doses) followed by a two-week recovery period. There were no drug-related clinical signs and changes to body weight, food consumption, ophthalmoscopy, clinical pathology, urinalysis, semiology or organ weights up to the level of 700 IU FVIII/kg. A specific re-evaluation of brain and spinal cord was conducted with regard to determination of any vacuolizations possibly caused by PEG. No findings indicative of any histopathological changes in the brain or spinal cord in animals receiving ADYNOVI were reported and the absence of any vacuolization in these organs could be confirmed. In sum, the NOAEL of ADYNOVI in rats was 700 IU FVIII/kg after 15 every other day injections for 29 days. In a pivotal repeat dose toxicity study in cynomolgus monkeys (Study 1933-018) 2 lots of ADYNOVI at dose levels of 150, 350 or 700 IU FVIII/kg were administered intravenously to the animals every 5 days for a period of 4 weeks (6 applications in total). There were no signs of toxicity or mortalities throughout the experimental period at any dose level. Minor findings like a decrease in red blood cell parameters (RBC, HGB, HCT), as well	In the repeat dose toxicity study in Cynomolgus monkey, two animals showed vacuolation in the kidney in the mid dose group (350IU/kg). The vacuolations did not recover after 2 weeks. The human relevance of kidney vacuolation observed in the preclinical study is unknown. Nonclinical data are limited to 1 month exposure and no studies in juvenile animals were conducted with ADYNOVI. Thus, it was not possible to conclude on the potential risks of PEG accumulation in various tissues/organs relevant for chronic use of ADYNOVI.

Key Safety Findings	Relevance to human usage
as a corresponding increase in reticulocyte counts together with bloody emesis (1 monkey of the mid dose, 2 animals out of the high dose group) or hematoma (1 monkey of the low dose, 1 of the mid dose and 1 monkey out of the high dose group), and a prolonged aPTT in all animals treated with ADYNOVI were noted during the last week of dosing. These observations were likely caused by the development of cross-reactive neutralizing anti-FVIII antibodies against endogenous FVIII which probably caused a partial reduction in cynomolgus monkey FVIII activity. A partial recovery for aPTT was noted until Day 12 of the recovery phase. There were no macroscopic and microscopic findings due to effects of ADYNOVI. Specific histopathological re-examination of brain and spinal cord confirmed the absence of any vacuolization in these organs. As expected for a heterologous human protein drug, repeated doses of ADYNOVI resulted in the formation of anti-drug antibodies specific for human FVIII or PEG and neutralizing for FVIII activity in animal models. The formation of antibodies against ADYNOVI is an expected immune reaction after repeated application of heterologous human proteins to cynomolgus monkeys, which is also well known for non-PEGylated FVIII products. Formation of anti-PEG antibodies did not result in any adverse reaction. Thus, the NOAEL for this study was the dose of 700 IU FVIII/kg.	
Reproductive/developmental toxicity	
Nonclinical studies on reproductive and developmental toxicity of ADYNOVI were not conducted. Due to the risk of incompatibility reactions based on an antigen-antibody reaction, reproductive and developmental toxicity studies would not be representative for the situation in humans. Moreover, it is well known that drugs with a molecular weight >500 Da often have incomplete transfer across the placenta and drugs >1000 Da cross very poorly. ADYNOVI is a large protein with a molecular weight of 280 kDa with several copies of a 20 kDa PEG attached. Therefore, it is expected to have only limited, if any, access to the conceptus or interaction with intracellular organelles including DNA. Additionally, protein replacement drugs which have a molecular structure identical to the endogenous human protein and are administered at levels intended to return the patient to a normal physiologic state are considered to be of reduced concern with the administration.	It is not known whether ADYNOVI can affect the reproductive capacity or cause fetal harm when given to pregnant women. It is unknown if ADYNOVI will be excreted in human milk.

Key Safety Findings	Relevance to human usage
Finally, studies on reproductive and developmental toxicity are regarded to be only of minor relevance for FVIII drug products since the majority of the haemophilia A patients would be males.	
Nephrotoxicity	
Studies on the nephrotoxic potential of ADYNOVI have not been performed. Please refer to repeat-dose toxicity above.	Not applicable
Hepatotoxicity	
Studies on the hepatotoxic potential of ADYNOVI have not been performed. Please refer to repeat-dose toxicity above.	Not applicable
Genotoxicity	
Studies on the genotoxic potential of ADYNOVI have not been performed. Genotoxicity studies are not applicable to the assessment of safety of biotechnology-derived pharmaceuticals such as PEGylated recombinant Factor VIII per ICH S6(R1), "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals".	Its mechanism of action and nature do not suggest that ADYNOVI interacts directly with the DNA or any other chromosomal material and hence this biological product is not considered to have any genotoxic potential. Therefore, genotoxicity studies are not warranted, and the standard battery of *in vitro* and *in vivo* tests has not been conducted.
Carcinogenicity	
Nonclinical studies have not been conducted with ADYNOVI to assess its mutagenic or carcinogenic potential. As stated in the regulatory guidance ICH S6(R1), "Guidance for Industry. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals", carcinogenicity testing of biological products is not required unless there is cause for concern. In addition, no proliferative activity was observed on histopathological examination of selected tissues from monkeys treated over a 28-day period at doses of 150, 350 and 700 IU FVIII/kg. Therefore, due to the lack of concern for the carcinogenic potential of ADYNOVI, no carcinogenicity studies have been conducted or are planned.	ADYNOVI is a recombinant protein and is not considered to be mutagenic nor clastogenic, or have any carcinogenic potential based on the pharmacological mode of action (e.g., immunosuppressive or proliferative activities).
Safety pharmacology:	
The thrombogenic potential of ADYNOVI in rabbits was comparable to that of ADVATE. Both lots of	Assessment of safety pharmacology in rabbits and cynomolgus monkeys supports the

Key Safety Findings	Relevance to human usage
ADYNOVI given at single intravenous infusions were well tolerated in the conscious telemetered cynomolgus monkey and did not cause any adverse clinical, cardiovascular or respiratory effects up to a dose of 600 IU FVIII/kg.	conclusion that ADYNOVI is safe for human use.
Other toxicity-related information or data:	
Local Tolerance	
Local tolerance was assessed during repeat dose toxicity studies in rats (Study 8202366) and cynomolgus monkeys. Microscopic findings at injection sites of animals were comparable with controls and were consistent with a normal response expected after intravenous injection. One additional study in rabbits was performed to investigate local tolerance of ADYNOVI at a potency of 2000 IU FVIII/5 mL vial. ADYNOVI with a nominal potency of 2000 IU FVIII/5 mL vial was well tolerated after intravenous (intended clinical administration route) intra-arterial and paravenous administration.	ADYNOVI was well tolerated after intravenous (intended clinical administration route), intra-arterial and paravenous administration (possible misapplications) in animal studies and should express similar profile for local tolerance in humans.
Immunogenicity	
Results obtained in comparative immunogenicity studies demonstrate that ADYNOVI and ADVATE have a similar FVIII immunogenicity profile. Two lots of ADYNOVI containing different aggregate levels expressed a similar FVIII immunogenicity profile compared to ADVATE in 2 different haemophilic mouse models. ADVATE has a proven safety profile in patients. ADYNOVI should express a similar safety profile in patients because ADYNOVI and ADVATE express similar FVIII immunogenicity profiles in nonclinical animal and in vitro models.	ADYNOVI should express a similar safety profile in patients because ADYNOVI and ADVATE express similar FVIII immunogenicity profiles in nonclinical animal and in vitro models.
Assessment of toxicity of excipients in ADYNOVI Final Drug Product	
The excipients used in the ADYNOVI final drug product (FDP) (namely, mannitol, trehalose dehydrate, sodium chloride, histidine, tromethamine/trometamol, [Tris (hydroxymethyl)-aminomethane], calcium chloride dehydrate, polysorbate 80, and glutathione) have well characterized safety profiles (FDA 2000, FDA 2013, Richards 2002). Non-serious hypersensitivity reactions to Tween 80 (polysorbate 80) have been observed and described in the literature in both the nonclinical (intravenously in dogs [redacted]) and in clinical settings (intravenously [redacted]). There are no known toxicities due to other excipients comprising	The excipients used in the ADYNOVI FDP have well characterized safety profiles. Non-serious hypersensitivity reactions to Tween 80 (polysorbate 80) have been observed and described in the literature in both the nonclinical and clinical settings. There are no known toxicities due to other excipients in ADYNOVI. ADYNOVI is contraindicated in patients with hypersensitivity to the active substance or any of the excipients of ADYNOVI and with known allergic reactions to mouse or hamster proteins.

Key Safety Findings	Relevance to human usage
ADYNOVI FDP.	
PEG related toxicity	
Toxicity of PEG2ru20KCOOH, a metabolite which is expected to be liberated after catabolism of the protein part of PEG-FVIII and which was identified in the final ADYNOVI final drug product, was evaluated in a rat model. Intravenous administration of PEG2ru20KCOOH for 4 weeks at dose levels of 0.65, 6.5 and 65 mg/kg was well tolerated with no negative clinical observations, effects on BW or food consumption, ophthalmoscopy, clinical or anatomical pathology. The NOAEL of 65 mg/kg approximates the 10-fold average clinical upper end (80 IU/kg) life-time (70 years) PEG exposure or the 10 000-fold exposure from a single upper-end clinical dose of ADYNOVI. Based on the safety profiles of PEG and other PEGylated biopharmaceuticals, no adverse effects were identified that would be relevant for the clinical therapy with PEGylated rFVIII ADYNOVI. A mechanistic study was conducted to assess the effect of 20 kDa PEG acid (PEG) exposure to human monocyte-derived macrophages (MDMs) at 10 µg, 100 µg, 1 mg or 10 mg/ml PEG for 24 hours. Results indicate that PEG mediates statistically significant vacuolation of human monocyte-derived macrophages (MDMs) *in vitro* only at concentrations 10,000 times higher than the plasma PEG concentration expected after a single prophylactic dose of 80 IU/kg BW (~0.1 µg PEG/ml blood). No statistically significant functional differences were observed after 20 kDa PEG exposure to human MDMs in an *in vitro* phagocytosis assay or in the cytokine profile in unstimulated and LPS stimulated human MDMs. Based on these data, it can be concluded that *in vitro* vacuolated human MDMs maintain their viability and functionality after single exposure to PEG.	Nonclinical data are limited to 1 month exposure and no studies in juvenile animals were conducted with ADYNOVI. Thus, it was not possible to conclude on the potential risks of PEG accumulation in various tissues/organs relevant for chronic use of ADYNOVI. No functional impairment of macrophages was observed at exposure to 20 kDa PEG at concentrations up to 10,000 times higher than the plasma PEG concentration expected after a single prophylactic dose of 80 IU/kg BW.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Table SIII. 1: Duration of exposure

Cumulative for all indications (person time):		
Duration of exposure	**Patients**	**Person time[a]**
<1 m	18	174
1 to <3 m	19	1131
3 to <6 m	13	1810
6 to <9 m	22	4666
9 to <12 m	8	2486
12 to <15 m	105	44332
15 to <18 m	30	14858
18 to <21 m	19	11432
21 to <24 m	23	15734
24 to <27 m	17	13290
27 to <30 m	17	14662
30 to <33 m	19	18443
33 to <36 m	46	48164
36 to <39 m	18	20532
39 to <42 m	11	13593
42 to <45 m	11	14751
45 to <48 m	9	12768
48 to <51 m	39	59373
51 to <54 m	12	18956
54 to <57 m	3	4994
>=57 m	19	39254
Total person time	478	375393

(Studies 261101, 261201, 261202, 261203, 261204, 261302 and 261303: Safety Analysis Set)
[a]Number of days in Observation Period of Safety

Table SIII. 2: Age group and gender

Cumulative for all age/gender groups (person time):				
Age group	**Patients**		**Person time[a]**	
	Male	**Female**	**Male**	**Female**
<6 years	158	0	143987	0
6 to <12 years	37	1	27700	990
12 to <18 years	41	0	37103	0
18 to <65 years	241	0	165613	0
>=65 years	0	0	0	0
Total	477	1	374403	990

(Studies 261101, 261201, 261202, 261203, 261204, 261302 and 261303: Safety Analysis Set)
[a]Number of days in Observation Period of Safety
Cut off-date: 12-November-2024

Table SIII. 3: Ethnic origin

Hemophilia A		
Ethnic origin	**Patients**	**Person time[a]**
American Indian or Alaska Native	0	0
Asian - Bajau	1	604
Asian - Bidayuh	1	1013
Asian - Brunei	1	607
Asian - Burmese	1	452
Asian - Chinese	33	21483
Asian - Indian	13	10038
Asian - Japanese	10	7879
Asian - Kadazan	1	428
Asian - Korean	4	3129
Asian - Malay	37	34707
Asian - Melanau	1	654

Hemophilia A		
Ethnic origin	**Patients**	**Person time[a]**
Asian - Mongoloid	19	22056
Asian - Punjabi	0	0
Asian - Thai	7	10244
Asian - Multiple	4	1917
Asian - Unknown	1	7
Black or African American	13	8757
Native Hawaiian or Other Pacific Islander	0	0
White	315	241482
Other	11	6724
Multiple	5	3212
Unknown or Not Reported	0	0
Total	478	375393

(Studies 261101, 261201, 261202, 261203, 261204, 261302 and 261303: Safety Analysis Set)
[a] Number of days in Observation Period of Safety
Cut off-date: 12-November-2024

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Subject has known hypersensitivity towards mouse or hamster proteins, PEG or Tween 80 (hypersensitivity to Tween 80 listed as exclusion criteria in pivotal study 261201 only).	
Reason for exclusion:	As with any intravenous protein product allergic type hypersensitivity reactions are possible. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADYNOVI. The product also contains traces of mouse and hamster proteins.
Is it considered to be included as missing information?:	No
Rationale:	As with any product, hypersensitivity reactions are possible. Patients with hypersensitivity to the active substance, to the excipients or allergic reactions to mouse or hamster protein should avoid use of ADYNOVI.

FVIII inhibitory antibodies (≥ 0.4 BU using the Nijmegen modification of the Bethesda assay or ≥ 0.6 BU using the Bethesda assay) at screening or medical history of FVIII inhibitory antibodies greater to or equal to 0.4 or 0.6 BU depending on clinical study and/or assay (Bethesda or Nijmegen modification of the Bethesda assay) at any time prior to screening.	
Reason for exclusion:	Subjects with FVIII inhibitors at screening cannot be evaluated for product-related immunogenicity or for efficacy. FVIII inhibitors partially or completely neutralize FVIII activity in plasma which makes haemostatic efficacy evaluation impossible.
Is it considered to be included as missing information?:	No
Rationale:	Subjects with low titer FVIII inhibitors may continue receiving FVIII concentrates in higher doses.

Diagnosis of an inherited or acquired defect other than haemophilia A	
Reason for exclusion:	Clinical studies with ADYNOVI focused on patients with congenital haemophilia A. Other haemostatic

Diagnosis of an inherited or acquired defect other than haemophilia A	
	disorders (acquired haemostatic disorders) may contribute to impaired clotting and may mask the ability to determine the efficacy of the product. Patients with other haemostatic disorders or comorbidities (e.g., acquired haemophilia A and the elderly) may be at increased risk for thromboembolic events.
Is it considered to be included as missing information?:	No
Rationale:	ADYNOVI is indicated for only haemophilia A to replace the missing factor FVIII. Use in patients with a history of other haemostatic disorders is not contraindicated; however, the benefits and risks of using the product should be carefully weighed against the patient's clinical condition.

Recent use of another PEGylated drug	
Reason for exclusion:	Subjects with recent use of another PEGylated product cannot be evaluated for product- related safety or efficacy.
Is it considered to be included as missing information?:	No
Rationale:	In the post-marketing setting, patients with recent exposure to another PEGylated product may receive other PEGylated FVIII concentrates provided there are no concurrent severe allergic reactions to PEG, ADYNOVI or the excipients.

Severe chronic hepatic dysfunction (e.g., ≥ 5 times the upper limit of normal alanine aminotransferase (ALT) at screening or a documented INR > 1.5)	
Reason for exclusion:	Altered liver function may contribute to impaired or delayed coagulation.
Is it considered to be included as missing information?:	No
Rationale:	Patients with altered hepatic function may benefit from ADYNOVI to aid in the treatment of bleeding. The benefits and risks of using the product should be carefully weighed against the patient's clinical condition.

[redacted]

Severe renal impairment (serum creatinine > 2.0 mg/dL) at screening	
Reason for exclusion:	Altered renal function may contribute to impaired coagulation or coagulation complications.
Is it considered to be included as missing information?:	No
Rationale: Provide rationale if not included as missing information.	Patients with altered renal function may benefit from ADYNOVI to aid in the treatment of bleeding. The benefits and risks of using the product should be carefully weighed against the patient's clinical condition.

SIV.2. LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: - Patients with hepatic impairment - Patients with renal impairment - Patients with cardiovascular impairment - Immunocompromised patients - Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program. Patients with severe chronic hepatic dysfunction (e.g., ≥5 times the ULN ALT at screening or a documented INR >1.5) were excluded from clinical studies with ADYNOVI. Subjects with hepatic dysfunction within the limits above were included in studies. Subjects with severe renal impairment (serum creatinine > 2.0 mg/dL) at screening were excluded from clinical studies with ADYNOVI. Clinical studies with ADYNOVI included subjects with severe (FVIII <1%) haemophilia A but did not include subjects with moderate or mild haemophilia A (FVIII ≥ 1%).
Population with relevant different ethnic origin	Please refer to Table SIII. 3 for Exposure by Ethnic Origin.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other - Children - Geriatric	Please refer to Table SIII. 2 for Clinical Study exposure by age group. Please refer to Table SIII. 2 for Clinical Study exposure by age group. Clinical studies with ADYNOVI did not include elderly subjects (greater than or equal to 65 years of age). Therefore, no analyses of an effect of intrinsic factors on PK such as age were conducted. Of note, subjects up to 75 years of age in the surgery study (261204) and the continuation study (261302). While approximately half of new inhibitors (49%) present before the patient is 5 years of age, the incidence of inhibitors initially declines with increasing age before rising to a second peak of 10.49 new inhibitors per 1000 patient-years at risk in patients ≥ 60 years of age[redacted]. Results of data on any elderly patients will be provided as they are received.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1. POST-AUTHORISATION EXPOSURE

SV.1.1. Method used to calculate exposure

The following equation was used to estimate the number of patients exposed to ADYNOVATE during the reporting interval:

Total Units Sold = (No)(Do) + (Np)(Dp)

Where:

No = number of patients-years in patients using on-demand treatment only

Do = Average total dose of ADYNOVATE used by a patient during 1 year of on-demand treatment, based on an average weight of 73 kilograms

Np = number of patients-years in patients using prophylaxis treatment

Dp = Average total dose of ADYNOVATE used by a patient on prophylaxis for 1 year, based on an average weight of 73 kilograms

SV.1.2. Exposure

Based on the above methodology, the patient exposure can be estimated to be 5,516,022,490 IUs cumulatively, corresponding to approximately 18,399.94 (4,040.62 using on-demand treatment and 14,359.32 using prophylactic treatment) PY treatment cumulatively. The true estimated number of patients will depend on the proportion of on-demand to prophylactic use in a given population.

Table SV.1: Estimate of Post-authorization Cumulative Patient Exposure[a]

Formula	**Cumulative (Till 31-October-2024)**	
	Calculation using IUs sold	**Total [PY]**
Average treatment dose (IU)	4,040.62 IU* on-demand	14,359.32 IU† on prophylaxis
IU sold	5,516,022,490	
On-demand [PY] = (Sales in IU/299,784.6)*0.2196	On-demand [PY] = (5,516,022,490/299,784.6) *0.2196 = 4040.62	4,040.62
Prophylaxis [PY] = (Sales in IU/299,784.6)*0.7804	Prophylaxis [PY] = (5,516,022,490/299,784.6) *0.7804 = 14,359.32	14,359.32
Total Number of PYs = On-demand [PY] + Prophylaxis [PY]	4040.62 + 14,359.32 = 18,399.94	18,399.94

[a] Data up to 31-October-2024 has been included
* Per bleeding episode based on data from [redacted], † per infusion based on data from [redacted]

Table SV.2: Post-authorisation exposure: Non-Interventional Studies

Study	**Adynovate (BAX855)**	**ADVATE**	**Total****
060902	99	399	402
061001	86	918	954

[redacted]

Study	Adynovate (BAX855)	ADVATE	Total**
TAK660-403	207	0	207
261603	342	0	342
261601*	135	0	135
TAK-660-5002*	15	0	15
Total	**884**	**1,317**	**2,055**

Data cut-off 12-November-2024
*Data from 2 Japanese studies (TAK-660-5002; 261601) are included as of 12-November-2024.
**Numbers in total column represent unique subjects

Table SV.3: Cumulative Exposure Estimate by Age Group and Gender from Non- interventional Studies

	Adynovate (BAX855)			ADVATE		
Study*#	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
< 6 years	51	0	51	231	1	232
6 years to < 12 years	87	0	87	248	1	249
12 to <18 years	95	1	96	150	0	150
18 to <65 years	611	3	614	667	0	667
>=65 years	30	0	30	19	0	19
Unknown (Not available)	6	0	6	0	0	0
Total	**880**	**4**	**884**	**1,315**	**2**	**1,317**

Data cut-off 12-November-2024, *Studies included 060902, 061001, 261603, TAK66-403, 261601, TAK-660-5002
#Data from 2 Japanese studies (TAK-660-5002; 261601) are included as of 12-November-2024

Table SV.4: Cumulative Exposure Estimate by Racial Group from Non-Interventional Studies

Race*#	Adynovate (BAX855)	ADVATE
African	0	1
African American	0	29
Asian	173	174
Caucasian	159	923
Hispanic	6	7
Missing	344	87
Not Applicable - Not collected per local regulations	13	0

Race*#	**Adynovate (BAX855)**	**ADVATE**
Other	14	79
Unknown	18	17
White	157	0
Total	**884**	**1,317**

Data cut-off 12-November-2024, *Studies included 060902, 061001, 261603, TAK66-403, 261601, TAK-660-5002
#Data from 2 Japanese studies (TAK-660-5002; 261601) are included as of 12-November-2024

Table SV.5: Cumulative Exposure Estimate for Pregnant/Lactating Women from Non-Interventional Studies

Category**	**Adynovate (BAX855)**	**ADVATE**
Pregnant/Lactating Women	1*	0

Data cut-off 12-November-2024
*[redacted]: This case was identified for study 261603, however was not included in the table since this was Pregnancy of partner case, with no adverse event reported.
**Studies included 060902, 061001, 261603, TAK66-403.

[redacted]

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for misuse of ADYNOVI for illegal purposes is considered unlikely.

[redacted]

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

There are no risks associated with the use of ADYNOVI which would not be considered important for inclusion in the list of safety concerns in the RMP. Whether a risk is considered identified risk or potential risk would depend on the strength of evidence supporting the causal association with the medicinal product.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
Inhibitor formation	The formation of neutralizing antibodies (inhibitors) against FVIII is a known complication in the management of individuals with haemophilia A. In patients who develop inhibitors to FVIII, the condition may manifest itself as an insufficient clinical response and can lead to lack of effect, which may result in serious haemorrhage, which may be life-threatening or fatal if not treated.
Hypersensitivity reactions	Hypersensitivity, allergic reactions, and anaphylaxis may result in a serious medical condition or potentially lead to fatal outcomes. Signs of hypersensitivity reactions may include angioedema, chest tightness, dyspnea, wheezing, urticaria, signs of shock (e.g., hypotension) or pruritus.

Important Potential Risks	Risk-benefit impact
Thromboembolic events	Thrombotic events can vary in seriousness and result in a variety of outcomes. Deep vein thrombosis may resolve spontaneously with little sequelae while stroke and myocardial infarction may result in significant disability or death. Thrombotic events can vary in seriousness and result in a variety of outcomes. Deep vein thrombosis may resolve spontaneously with little sequelae while stroke and myocardial infarction may result in significant disability or death.
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)	The long-term effect of PEG exposure in humans is not known. Very little information on neurological or renal toxicity in a pediatric haemophilia population < 12 years of age is available other than through case reports.

[redacted]

Important Potential Risks	Risk-benefit impact
Anti-PEG FVIII antibodies	Antibodies against PEG have been seen in healthy individuals and PWH without any signs of disease [redacted]. Other reported effects could be a reduction in the efficacy of a therapeutic agent or hypersensitivity reactions.
Overdosing (thrombosis) when switching to ADYNOVI from another FVIII product or underdosing (lack of efficacy/bleeding) when switching from ADYNOVI to another FVIII product	High and sustained levels of FVIII activity have been statistically associated with arterial or venous thrombosis in individuals with underlying risk factors for thrombosis. Underdosing may not provide adequate FVIII replacement, insufficient FVIII activity may manifest itself as a lack of therapeutic response. Depending on the severity and nature of the overdosing or underdosing, patients may require medical intervention and costly prolonged hospitalization.

Missing Information	Risk-benefit impact
Use in patients ≥ 65 years of age	No clinical data on use in patients ≥ 65 years of age.
Use in PUPs	The safety and efficacy of ADYNOVI in PUPs has not yet been established.
Use of ADYNOVI for ITI	No clinical data for use of ADYNOVI in ITI are available.
Use during pregnancy and lactation	No clinical studies have been done in women, including those who may be pregnant and/or breastfeeding.

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Missing information of "Use in PUPs" and "Use of ADYNOVI for ITI" has been removed after the completion of paediatric PUP study 261203 as this provides sufficient information on use in PUPs and ITI. No further additional PV activities are required to further classify the safety in these patient populations.

[redacted]

SVII.3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Inhibitor formation	
Potential mechanisms:	FVIII inhibitors neutralize FVIII by impairing the binding of FVIII to one of its partners by steric hindrance and thereby blocking its biologic function or by other mechanisms such as catalytic degradation of FVIII. Binding antibodies against FVIII or against PEG [redacted] have been shown to potentially accelerate clearance of therapeutic protein or inhibit its function.
Evidence source(s) and strength of evidence:	Scientific Literature, SmPC, Company Core Safety Information (CCSI), Clinical trials, Global Safety Database.
Characterisation of the risk:	**Frequency with 95% CI** Results of Phase 1 study 261101 demonstrated that no subject developed FVIII inhibitors ≥0.4 BU. None of the 19 subjects treated with ADVATE and ADYNOVATE had detectable binding antibodies with confirmed specificity to FVIII, PEG-FVIII or PEG at any time point during the study. Results of pivotal Phase 2/3 study 261201 demonstrated no positive titers for FVIII inhibitory antibodies ≥0.6 BU. None of the subjects SAS output developed a persistent binding antibody response to FVIII, PEG-FVIII or PEG. Seven subjects tested as negative at screening developed transient IgG binding antibodies against FVIII or PEG-FVIII at 1 or 2 consecutive study visits after exposure to ADYNOVATE. Antibodies were transient and not detectable at subsequent visits or at completion of the study. No binding antibodies against CHO protein were detected. Results of surgery study 261204 demonstrated no inhibitory antibodies to FVIII, no persistent binding antibodies subclass to FVIII, PEG-FVIII, or PEG. One transient positive IgG binding antibody to FVIII was seen at the completion/termination visit, which was negative at screening. The same subject had a pre-existing IgG binding antibody to PEG-FVIII at screening and at the completion/termination visit, which did not increase during the study. None of the subjects developed binding antibodies to CHO proteins. There have been no reports of lack of efficacy in clinical trials with ADYNOVATE to date. **Seriousness/Outcomes** Inhibitor formation can lead to lack of effect, which may result in serious hemorrhage, which may be

Important Identified Risk: Inhibitor formation	
	life-threatening or fatal if not treated. **Nature of risk** Inhibitor formation may result in lack of response to treatment and subsequent acute bleeding episodes potentially affecting joints, muscles, mucosa, body activities, and the central nervous system. If lack of effect due to neutralizing antibodies occurs, potential outcomes may range from asymptomatic factor VIII activity level changes to life-threatening or fatal hemorrhage if untreated. **Background incidence/prevalence** The incidence of inhibitor formation is estimated to be as high as 33% in PUPs with moderate or severe hemophilia A[redacted]. The prevalence of inhibitors is reported to range from 5% to 13% in persons with hemophilia (PWH) depending on severity of disease [redacted]. The difference between the incidence and prevalence of inhibitor formation has to do with the disappearance of transient low-titer inhibitors and successful tolerization of others[redacted]. Approximately half of new inhibitors (49%) present before patients reach 5 years of age with a rate of 64 new inhibitors per 1000 PY at risk. Following the initial peak, the incidence of inhibitors declines with increasing age before rising to a second peak of 10 new inhibitors per 1000 PY at risk in patients 60 years of age or older). Often, these patients suddenly develop recurrent bleeding and may have a factor level that measures below their historical baseline level. When patients with mild or moderate haemophilia develop inhibitors, it is usually in association with intensive factor exposure such as with a surgical or traumatic challenge [redacted]. In PWH inhibitor formation may be seen as lack of effect, and the acquisition of inhibitors is one of the most challenging problems associated with the treatment of haemophilia. In an observational study it was estimated that about 91% (349 of 381) of the haemophiliac population with inhibitors were due to inhibitors to FVIII[redacted]. **CLINICAL TRIAL EXPERIENCE:** A search of the GSDB, as of 12-November-2024, retrieved 13 cases with 13 SAEs of inhibitor formation. Twelve events were from clinical trial 261203 and 1 from 261303. The PTs were Factor VIII inhibition (n=12) and Inhibiting antibodies positive (n=1). The outcome of the events was Not Recovered/Not Resolved (n=4), Recovered/Resolved (n=8) and Unknown (n=1). In pediatric population, 12 cases with 12 SAEs of inhibitor formation were reported. The reported PTs

[redacted]

Important Identified Risk: Inhibitor formation	
	were Factor VIII inhibition (n=11) and Inhibiting antibodies positive (n=1). The outcome of the events was recovered/resolved (n=7), not recovered/not resolved (n=4) and unknown (n=1). No SAEs were retrieved from clinical trial sources in geriatric patients and pregnant and breast-feeding women. **POST-MARKETING EXPERIENCE:** A search of the GSDB, as of 12-November-2024, retrieved 164 cases with 170 events (159 serious and 11 non-serious) of inhibitor formation. Characterisation of these cases based on source type is presented below. **Post Marketing Study Sources**: Cumulatively, 97 cases with 98 events (3 serious and 95 non-serious) of inhibitor formation were retrieved from post-marketing study sources. The reported PTs were Drug ineffective (n=74), Factor VIII inhibition (n=6), Therapeutic product effect incomplete (n=5), Therapeutic product effect decreased (n=4), Anti-factor VIII antibody positive (n=3), Therapeutic product effect delayed (n=2), Drug half-life reduced (n=1), Device failure (n=1), Device defective (n=1) and Treatment failure (n=1). The outcome of the events was not recovered/not resolved (n=6), recovering/resolving (n=1), recovered/resolved (n=10) and unknown (n=81). **Spontaneous Sources**: Cumulatively, 64 cases with 69 events (61 serious and 8 non-serious) of inhibitor formation were retrieved from spontaneous sources. In 1 serious case with 1 event, the suspect product was Helixate Nexgen, and the case is excluded from further analysis. For the remaining 68 events, reported PTs were Factor VIII inhibition (n=24), Drug ineffective n=20), Anti-factor VIII antibody positive (n=5), Drug half-life reduced (n=5), Therapeutic product effect incomplete (n=2), Therapeutic response decreased (n=2), Therapeutic response delayed (n=2), Therapeutic product effect decreased (n=2), Anti factor VIII antibody increased (n=1), Device failure (n=1), Drug level decreased (n=1), Inhibiting antibodies positive (n=1), Device defective (n=1) and Therapy non-responder (n=1). The outcome of the events was not recovered/not resolved (n=6), recovered/resolved (n=17), recovering/resolving (n=3), and unknown (n=42).

Important Identified Risk: Inhibitor formation	
	Pediatric population: Cumulatively, in pediatric population 57 cases with 60 events (56 serious and 4 non-serious) of inhibitor formation were retrieved. In 1 serious case with 1 event, the suspect product was Helixate Nexgen, and the case is excluded from further analysis. Of these 56 cases (59 events), 31 cases (32 events) were retrieved from post-marketing study and 25 cases (27 events) were retrieved from spontaneous sources. The reported PTs were Drug ineffective (n=26), Factor VIII inhibition (n=15), Anti-factor VIII antibody positive (n=5), Drug half-life reduced (n=4), Therapeutic product effect incomplete (n=3), Therapeutic response decreased (n=2), Device failure (n=2), Anti factor VIII antibody increased (n=1) and Therapeutic product effect delayed (n=1). The outcome of the events was not recovered/not resolved (n=8), recovering/resolving (n=3), recovered/resolved (n=6) and unknown (n=42). **Geriatric population:** Cumulatively, in geriatric patients 5 cases with 5 serious events of inhibitor formation were retrieved. Of these 5 cases, 1 case was retrieved from post-marketing study and 4 cases were retrieved from spontaneous sources. The reported PTs were Factor VIII inhibition (n=2), therapeutic product effect incomplete (n=1), drug ineffective (n=1) and drug level decreased (n=1). The outcome of the events was not recovered/not resolved (n=1), recovered/resolved (n=3) and unknown (n=1). **Pregnant and breast-feeding women:** A search of the GSDB retrieved no cases for pregnant and breast-feeding women.
<u>Risk factors and risk groups:</u>	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 [redacted]. 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 [redacted]. 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[redacted]. Approximately half of the new inhibitors (49%) presented before the patient

[redacted]

Important Identified Risk: Inhibitor formation	
	was 5 years of age [redacted]. 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[redacted]. 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)[redacted].
Preventability:	There is no documented method to prevent FVIII inhibitor formation. However, patients using ADYNOVATE should be regularly monitored for the development of FVIII inhibitors. The Bethesda inhibitor assay should be performed if expected FVIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of ADYNOVATE. The administration of additional antihemophilic factor concentrate may neutralize a lower titer inhibitor and may permit an appropriate hemostatic response. If there is a lack of response, treatment or prevention of bleeding may require the use of alternative therapeutic approaches and agents.
Impact on the risk-benefit balance of the product:	Inhibitors may result in lack of response to treatment and subsequent acute bleeding episodes potentially affecting joints, muscles, mucosa, body cavities, and the central nervous system, which may require additional therapies (e.g., central venous access device placement). Left untreated, the patient could experience fatal uncontrolled bleeding.
Public health impact:	Uncontrolled bleeding episodes may result in hospitalization or life-threatening injury. Once an inhibitor exists, there may be lifelong costly therapy, e.g., with bypassing agents. Injury may also result in loss of days of school and/or work, persistent disability, and impact upon caregivers.

[redacted]

Important Identified Risk: Hypersensitivity Reactions	
Potential mechanisms:	Potential mechanisms include an immune mediated response to ADYNOVATE or any of the excipients of the product. Among patients treated with FVIII concentrates (e.g., ADVATE), serious hypersensitivity reactions have been occasionally observed.
Evidence source(s) and strength of evidence:	CCSI, Scientific literature, clinical trials, Global Safety Database.
Characterisation of the risk:	**Frequency with 95% CI** There were non-serious reported events of Rash and Hypersensitivity in <6-year-old previously untreated subject from the PUP trial study 261203. These events of Rash and Hypersensitivity were considered to be ADRs and the CCSI was updated on 24-June-2016. The occurrence of severe allergic reactions is being evaluated as part of the ADYNOVATE clinical development program. **Seriousness/Outcomes** Hypersensitivity, allergic reactions, and anaphylaxis may result in a serious medical condition or potentially lead to fatal outcomes. Signs of hypersensitivity reactions may include angioedema, chest tightness, dyspnea, wheezing, urticaria, signs of shock (e.g., hypotension) or pruritus. **Severity and nature of risk** Allergic reactions can range from a rash to fatal anaphylactic reactions. **Background incidence/prevalence** The incidence of anaphylaxis does not appear to vary significantly between countries. Rates globally range from 1-3 cases per 10 000 in the general population[redacted]. However, hypersensitivity drug reactions represent approximately one-third of ADRs, which can affect 7% of the general population and up to 20% of hospitalized patients[redacted]. Allergic reactions to rFVIII have been reported to occur rather infrequently in less than 1% of patients[redacted]. However, the exact incidence and prevalence of hypersensitive reactions associated with rFVIII remains unknown at this time. **CLINICAL TRIAL EXPERIENCE:** A search of the GSDB as of 12-November-2024 retrieved 2 SAEs from clinical trial source for ADYNOVATE. Both the cases were reported in pediatric population. The PTs were Rash and Immune thrombocytopenia (n=1 each). The outcome of the events was recovered/resolved (n=2). No SAEs were retrieved from clinical trial sources in geriatric patients and pregnant and breast-feeding

[redacted]

Important Identified Risk: Hypersensitivity Reactions	
	women. **POST-MARKETING EXPERIENCE**: A search of the GSDB as of 12-November-2024, retrieved 66 cases with 85 events (21 serious and 64 non-serious) of hypersensitivity reactions. Characterization of these cases based on source type is presented below. **Post-Marketing Study Sources:** Cumulatively, 32 cases with 49 events (8 serious and 41 non-serious) of hypersensitivity reactions were retrieved from post-marketing study sources. The reported PTs were Swelling face (n=12), Rash (n=6), Eczema (n=4), Lip swelling (n=3), Eye swelling (n=3), Rhinitis allergic (n=2), Infusion related reaction (n=2), Infusion site rash (n=2), and the remaining PTs reported with single frequency included Dermatitis allergic, Hypersensitivity, Rash macular, Drug hypersensitivity, Pharyngeal swelling, Swollen tongue, Rash erythematous, Anaphylactic shock, Rash pruritic, Circulatory collapse, Dermatitis atopic, Periorbital swelling, Urticaria, Injection related reaction and Injection site rash. The outcome of the events was not recovered/ not resolved (n=4), recovered/ resolved with sequelae (n=1), recovering/resolving (n=7), recovered/ resolved (n=22) and unknown (n=15). **Spontaneous Sources:** Cumulatively, 34 cases with 36 events (13 serious and 23 non-serious) of hypersensitivity reactions were retrieved from spontaneous sources. The reported PTs were Anaphylactic reaction (n=8), Urticaria (n=5), Hypersensitivity (n=5), Infusion related reaction (n=4), Rash (n=2), Drug hypersensitivity (n=2), Polymers allergy (n=2), Pharyngeal swelling (n=2), Swollen tongue (n=1), Injection site rash (n=1), Skin reaction (n=1), Allergic cough (n=1) and Swelling face (n=1). The outcome of the events was not recovered/not resolved (n=2), recovered with treatment (n=1), recovering/resolving (n=4), recovered/resolved (n=20) and unknown (n=9). **Pediatric population:** Cumulatively, in pediatric population 37 cases with 47 events (11 serious and 36 non-serious) of hypersensitivity reactions were retrieved. Of these 37 cases (47 events), 21 cases (30 events) were retrieved from post-marketing study, 15 cases (16 events) were retrieved from spontaneous sources and 1 case (1 event) was retrieved from literature spontaneous. The reported PTs were Swelling face (n=9), Anaphylactic reaction (n=5), Rash (n=4), Pharyngeal swelling (n=3),

Important Identified Risk: Hypersensitivity Reactions	
	Eczema (n=3), Hypersensitivity (n=3), Infusion related reaction (n=2), Urticaria (n=2), Infusion site rash (n=2), Eye swelling (n=2), and the remaining PTs reported with single frequency included Rash erythematous, Drug hypersensitivity, Rhinitis allergic, Injection site rash, Dermatitis allergic, Lip swelling, Rash macular, Periorbital swelling, Dermatitis atopic, Anaphylactic shock, Allergic cough and Polymers allergy. The outcome of the events was not recovered/ not resolved (n=3), recovered/ resolved with sequelae (n=1), recovering/resolving (n=8), recovered/resolved (n=23), and unknown (n=12). **Geriatric population:** Cumulatively, in geriatric patients 4 cases with 11 events (8 non-serious and 3 serious) of hypersensitivity reactions were retrieved. Of these 4 cases, 2 cases were retrieved from post-marketing study and 2 case from spontaneous source. The reported PTs were Rash (n=2), Circulatory collapse (n=1), Eye swelling (n=1), Infusion related reaction (n=1), Lip swelling (n=1), Rash pruritic (n=1), Swelling face (n=1), Vancomycin infusion reaction (n=1), Swollen tongue (n=1), Urticaria (n=1). The outcome of the events was: not recovered/not resolved (n=2), recovered/resolved (n=7) and recovering/resolving (n=2). **Pregnant and breast-feeding women**: A search of the GSDB retrieved no cases for pregnant and breast-feeding women.
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.
Preventability:	Careful intake of patients' medical history for allergic/hypersensitivity reactions. Premedication with antihistamines in atopic patients and patients with allergic reactions in their medical history. Note history of past hypersensitivity reactions in the patient records. ADYNOVATE is contraindicated in patients with known hypersensitivity reaction to the active substance or any of the excipients and for patients with known allergic reactions against mouse or hamster proteins. Immediately discontinue administration and initiate appropriate treatment if allergic or anaphylactic-type reactions occur. Treatment may include steroids and antihistamines.

[redacted]

Important Identified Risk: Hypersensitivity Reactions	
Impact on the risk-benefit balance of the product:	An allergic reaction or anaphylaxis may result in a serious medical condition or potentially lead to a fatal outcome.
Public health impact:	Depending on the severity and nature of the hypersensitivity reaction, patients may require medical intervention and hospitalization.

Important Potential Risk: Thromboembolic Events	
Potential mechanisms:	High and sustained levels of FVIII activity have been statistically associated with arterial or venous thrombosis in individuals with underlying risk factors for thrombosis[redacted]. 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.
Evidence source(s) and strength of evidence:	Literature, Global Safety Database
Characterisation of the risk:	**Frequency with 95% CI** There was no clinical evidence of thrombotic complications in any of the subjects throughout all clinical studies. **Seriousness/Outcomes** Thrombotic events can vary in seriousness and result in a variety of outcomes. Deep vein thrombosis may resolve spontaneously with little sequelae while stroke and myocardial infarction may result in significant disability or death. **Severity and nature of risk** Thromboembolic events may potentially result in a serious medical condition or fatal outcome. Blood clots may reduce blood supply to various organs such as the liver, brain, or kidney. Multiple organ failure may result. **Background incidence/prevalence** Unknown **CLINICAL TRIAL EXPERIENCE:** A search of the GSDB as of 12-November-2024 retrieved 1 SAE from clinical trial source in pediatric patient for ADYNOVATE. The reported PT was Vascular device occlusion. The outcome of the event was Recovered/Resolved (n=1). No SAEs were retrieved from clinical trial sources in geriatric patients and pregnant and breast-feeding women. **POST-MARKETING EXPERIENCE**: A search of the GSDB as of 12-November-2024,

Important Potential Risk: Thromboembolic Events	
	retrieved 21 cases with 23 events (21 serious and 2 non-serious) of thromboembolic events. Characterization of these cases based on source type is presented below. **Post-Marketing Study Sources:** Cumulatively, 12 cases with 12 events (serious and 2 non-serious) of thromboembolic events were retrieved from post-marketing study sources. The reported PTs were myocardial infarction (n=3), Venous thrombosis (n=2), Acute myocardial infarction (n=2), Thrombotic cerebral infarction (n=1), Cerebral infarction (n=1), Cerebrovascular accident (n=1), Deep vein thrombosis (n=1) and Embolism (n=1). The outcome of the events was recovering/resolving (n=2), recovered/ resolved with sequelae (n=1), recovered/resolved (n=8) and Unknown (n=1). **Spontaneous Sources:** Cumulatively, 8 cases with 10 events (all serious) of thromboembolic events were retrieved from spontaneous Sources. The reported PTs were Myocardial infarction (n=3) and the remaining PTs reported with single frequency included Shunt occlusion, Thrombotic stroke, Cardiac ventricular thrombosis, Thrombosis in device, Embolism venous, Acute myocardial infarction and Ischaemic stroke. The outcome of the events was fatal (n=3), recovered/resolved (n=3) and unknown (n=4). **Pediatric population:** Cumulatively, in pediatric population 1 case with 1 event (serious) of hypersensitivity reactions was retrieved. One (1) case (1 event) was retrieved from post-marketing study. The reported PT was Myocardial infarction. The outcome of the events was resolved. **Geriatric population:** Cumulatively, in geriatric patients 8 cases with 9 events (all serious) of thromboembolic events were retrieved. Of these 8 cases, 5 cases were retrieved from post-marketing study sources, 2 cases from spontaneous sources and 1 case from literature - Spontaneous. The reported PTs were Myocardial infarction (n=2) and the remaining PTs reported with single frequency included Embolism venous, Shunt occlusion, Cerebral infarction, Ischaemic stroke, Cerebrovascular accident, Acute myocardial infarction and Embolism. The outcome of the events was fatal (n=3), recovering/resolving (n=1), recovered/resolved (n=3) and unknown (n=2).

[redacted]

Important Potential Risk: Thromboembolic Events	
	Pregnant and breast-feeding women: A search of the GSDB retrieved no cases for pregnant and breast-feeding women.
Risk factors and risk groups:	Patients with liver disease, peri- and postoperative patients, newborn infants, or other patients at risk for thromboembolic events or DIC.
Preventability:	Clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing, particularly for risk patients.
Impact on the risk-benefit balance of the product:	Impact on the individual patient may vary depending on the severity of the thrombotic event. Depending on the severity, thrombotic events may result in significant disability or death.
Public health impact:	This may require prolonged hospitalization, costly treatment and can have life-threatening or fatal outcomes.

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)	
Potential mechanisms:	Unknown
Evidence source(s) and strength of evidence:	Literature, Preclinical safety data section 5.3 of the SmPC, Global Safety Database
Characterisation of the risk:	**Background incidence/prevalence** The long-term effect of PEG exposure in humans is not known. Very little information on neurological or renal toxicity in a pediatric hemophilia population <12 years of age is available other than through case reports. Because human immunodeficiency virus (HIV) and hepatitis C are comorbid conditions with hemophilia and may include antiviral therapy (i.e., acyclovir), neurological involvement with acyclovir has varied from confusion to coma[redacted]. A 16-year-old white hemophiliac boy with HIV infection[redacted] secondary to tainted coagulation factor VIII was treated with indinavir sulfate and developed gross hematuria, proteinuria, pyuria, and elevated serum creatinine within 1 month of starting indinavir sulfate therapy[redacted]. reported that exposure to nephrotoxic agents as therapy for HIV or hepatitis C may place the hemophilia patient at higher risk for renal disease.

[redacted]

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)	
	CLINICAL TRIAL EXPERIENCE: A search of the GSDB as of 12-November-2024 retrieved 4 SAEs from clinical trial source for ADYNOVATE. The reported PTs were Febrile convulsion (n=2), Liver injury (n=1) and Transaminases increased (n=1). The outcome of the events was recovered/resolved (n=4). Of these 4 SAEs from clinical trial, 2 SAEs were reported in pediatric patient. The PT was Febrile convulsion (n=2). The outcome of the event was Recovered/Resolved (n=2). No SAEs are retrieved from clinical trial sources in geriatric patients and pregnant and breast-feeding women. **POST-MARKETING EXPERIENCE**: A search of the GSDB, as of 12-November-2024, retrieved 75 cases with 97 events (57 serious and 40 non-serious) of potential effect of PEG accumulation. Characterization of these cases based on source type is presented below. **Post Marketing Study Sources**: Cumulatively, 48 cases with 62 events (34 serious and 28 non-serious) of long-term potential effect of PEG accumulation were retrieved from post-marketing study. The reported PTs were Dizziness (n=9), Haematuria (n=8), Hepatitis C (n=4), Seizure (n=4), Epilepsy (n=4), Hepatic steatosis (n=3), Renal failure (n=3), Acute kidney injury (n=2), Alanine aminotransferase increased (n=2), Hepatic neoplasm (n=2), Renal impairment (n=2) and Hepatic enzyme increased (n=2). The remaining PTs were reported with single frequency included Hepatic cirrhosis, Presyncope, Liver function test abnormal, Blood urea increased, Renal function test abnormal, Albumin urine present, Hypocalcaemia, Head discomfort, Nephrosclerosis, Hepatic cancer, Hepatic encephalopathy, Hepatitis, Dizziness exertional, Hepatitis B, Varices oesophageal, Hepatic function abnormal and Hepatic hypertrophy. The outcome of the events was fatal (n=2), not recovered/not resolved (n=14), recovering/resolving (n=6), recovered/resolved (n=24), and unknown (n=16).

	Spontaneous Sources: Cumulatively, 27 cases with 35 events (23 serious and 12 non-serious) of long-term potential effect of PEG accumulation were retrieved from spontaneous Sources. The reported PTs were Haematuria (n=10), Hepatic steatosis (n=5), Seizure (n=3), Dizziness (n=3), Hepatitis C (n=2), Hepatic failure (n=2) and the remaining PTs reported with single frequency included Liver abscess, Hepatic cirrhosis, Hepatocellular carcinoma, Head discomfort, Multiple sclerosis, Nephropathy, Hepatitis B, Unresponsive to stimuli, Demyelination and Hepatitis. The outcome of the events was fatal (n=5), not recovered/not resolved (n=5), recovered/resolved (n=17) and unknown (n=8). **Paediatric population**: Cumulatively, in pediatric patients 11 cases with 13 events (7 serious and 6 non-serious) of long-term potential effect of PEG accumulation were retrieved. Of these 11 cases (13 events), 5 cases (6 events) were received from post-marketing study and 6 cases (7 events) were retrieved from spontaneous sources. The PTs were Haematuria (n=6), Dizziness (n=3), Hepatic steatosis (n=1), Seizure (n=1), Unresponsive to stimuli (n=1) and Presyncope (n=1). The outcome of the events was recovered/resolved (n=10), recovering/resolving (n=1) and unknown (n=2). **Geriatric population**: Cumulatively, in geriatric patients 15 cases with 24 events (18 serious and 6 non-serious) of long-term potential effect of PEG accumulation were retrieved. Of these 15 cases, 9 cases (18 events) were retrieved from post-marketing study sources and 6 cases (6 events) were retrieved from spontaneous sources. The reported PTs were Renal failure (n=2), Hepatitis C (n=2), Renal impairment (n=2) and Acute kidney injury (n=2). The remaining PTs reported with single frequency included Haematuria, Liver function test abnormal, Dizziness, Hepatic cancer, Nephrosclerosis, Hepatic encephalopathy, Hepatitis B, Hepatic failure, Liver abscess, Hepatic function abnormal, Nephropathy, Blood urea increased, Dizziness exertional, Hepatic neoplasm, Hepatitis and Hepatic hypertrophy. The outcome of the events was fatal (n=3), not recovered/not resolved (n=5), recovering/resolving (n=5), recovered/resolved (n=8) and unknown (n=3).

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)	
	Pregnant and breast-feeding women: A search of the GSDB retrieved no cases for pregnant and breast-feeding women.
Risk factors and risk groups:	All patient populations are potentially exposed to PEG by way of consumer products and in parenteral and oral pharmaceuticals.
Preventability:	Unknown
Impact on the risk-benefit balance of the product:	Depending on the severity and nature of the reaction, patients may require medical intervention and hospitalization
Public health impact:	Potential for prolonged hospitalization, costly treatment and can have life-threatening or fatal outcomes.

Important Potential Risk: Anti-PEG-FVIII Antibodies	
Potential mechanisms:	Immune mediated response
Evidence source(s) and strength of evidence:	Literature, Global Safety Database
Characterisation of the risk:	**Frequency with 95% CI** 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. None of the 243 subjects considered in the immunogenicity risk assessment developed inhibitory antibodies to FVIII ≥0.6 BU/mL or persistent binding antibodies to FVIII, PEG-FVIII or PEG. Five subjects showed positive results for binding antibodies to PEG-FVIII, FVIII or PEG at study completion or at the time of the data cut-off. No conclusion can be drawn whether these antibodies are of transient or persistent nature. **Seriousness/Outcomes** Antibodies against PEG have been seen in healthy individuals and PWH without any signs of disease [redacted]. Other reported effects could be a reduction in the efficacy of a therapeutic agent or hypersensitivity reactions. **Severity and nature of risk** Lack of effect could result in serious hemorrhage,

[redacted]

Important Potential Risk: Anti-PEG-FVIII Antibodies	
	which may be life-threatening or fatal if not treated[redacted]. Hypersensitivity reactions can range from a rash to anaphylaxis and could also be life-threatening[redacted]. **Background incidence/prevalence** Recent analyses of serum sample from healthy individuals demonstrated a prevalence of anti-PEG antibodies in 44%–72%[redacted]. A recent publication[redacted] also reported the presence of circulating antibodies against PEG in a proportion of healthy individuals and in hemophilia patients who had not been treated with any pegylated biotherapeutics[redacted]. **CLINICAL TRIAL EXPERIENCE:** A search of the GSDB as of 12-November-2024 retrieved no SAEs from clinical trial source for ADYNOVATE. **POST-MARKETING EXPERIENCE:** A search of the GSDB, as of 12-November-2024, retrieved 11 cases with 11 serious events of Anti-PEG-FVIII Antibodies. Characterization of these cases based on source type is presented below. **Post Marketing Study Sources**: Cumulatively, 5 cases with 5 serious events of Anti-PEG-FVIII Antibodies were retrieved from post-marketing study sources. The reported PT was Anti factor VIII antibody positive (n=5). The outcome of the events was unknown (n=5). **Spontaneous Sources**: Cumulatively, 6 cases with 6 serious events of Anti-PEG-FVIII Antibodies were retrieved from spontaneous sources. The reported PTs were Anti factor VIII antibody positive (n=5) and Anti factor VIII antibody increased (n=1). The outcome of the events were unknown (n=5) and recovering/resolving (n=1). **Paediatric population**: Cumulatively, in pediatric patients 6 cases with 6 serious events were retrieved. Of these 6 cases, 3 cases were retrieved from Literature – Spontaneous, 2 cases were from literature spontaneous sources and 1 case was retrieved from spontaneous sources. The reported PTs were Anti factor VIII antibody positive (n=5) and Anti factor VIII antibody increased (n=1). The outcome of the events were unknown (n=5) and

Important Potential Risk: Anti-PEG-FVIII Antibodies	
	recovering/resolving (n=1). **Geriatric population**: Cumulatively, a search of the GSDB retrieved no cases for geriatric population. **Pregnant and breast-feeding women**: Cumulatively, a search of the GSDB retrieved no cases for pregnant and breast-feeding women.
Risk factors and risk groups:	Healthy individuals and PWH are routinely exposed to substantial amounts of PEG (lotions, creams, laxatives and biotherapeutics)
Preventability:	Note: history of exposure to PEG-containing products. Prescreen for the presence of antibodies against PEG.
Impact on the risk-benefit balance of the product:	Patients with pre-existing antibodies against PEG may experience a decrease therapeutic efficacy or experience allergic reactions[redacted].
Public health impact:	Depending on the severity and nature of the hypersensitivity reaction, patients may require medical intervention and hospitalization.

Important Potential Risk: Overdosing (thrombosis) when Switching to ADYNOVATE from Another FVIII Product or Underdosing (lack of efficacy/bleeding) when Switching from ADYNOVATE to Another FVIII Product	
Potential mechanisms:	High and sustained levels of FVIII activity have been statistically associated with arterial or venous thrombosis in individuals with underlying risk factors for thrombosis [redacted]. Insufficient FVIII activity may manifest itself as a lack of therapeutic response.
Evidence source(s) and strength of evidence:	Literature, Global Safety Database
Characterisation of the risk:	**Frequency with 95% CI** Unknown **Seriousness/Outcomes** Thrombosis may result in deep vein thrombosis which may resolve spontaneously with little sequelae while stroke and myocardial infarction may result in significant disability or death. Lack of efficacy may cause acute bleeding into joints or muscles or serious bleeds such as intracranial or gastrointestinal bleeding.

[redacted]

Important Potential Risk: Overdosing (thrombosis) when Switching to ADYNOVATE from Another FVIII Product or Underdosing (lack of efficacy/bleeding) when Switching from ADYNOVATE to Another FVIII Product	
	Severity and nature of risk Lack of effect or increased FVIII levels could result in serious hemorrhage or formation of thrombus respectively. Both may be life-threatening or fatal if not treated. **Background incidence/prevalence** Unknown **CLINICAL TRIAL EXPERIENCE:** A search of the GSDB as of 12-November-2024 retrieved 66 SAEs from clinical trial source. The reported PTs were Factor VIII inhibition (n=12), Haemarthrosis (n=9), Muscle haemorrhage (n=7), Haematoma (n=6), Haematoma muscle (n=3), Haemorrhage (n=3), Pharyngeal haemorrhage (n=2) and Subcutaneous haematoma (n=2), and the remaining PTs with single frequency included Enterocolitis haemorrhagic, Nail bed bleeding, Mouth haemorrhage, Epistaxis, Post procedural haematoma, Extradural haematoma, Intracranial haematoma, Haemophilic arthropathy, Cerebral haemorrhage, Traumatic haematoma, Gingival bleeding, Traumatic haemorrhage, Post procedural haemorrhage, Splenic haematoma, Tongue haemorrhage, Vascular device occlusion, Gastrointestinal haemorrhage, Cerebellar haematoma, Traumatic intracranial haemorrhage, Haemorrhage intracranial, Wound haemorrhage, Immune thrombocytopenia and Injection site haematoma. The outcome of the event was fatal (n=1), not recovered/not resolved (n=4), recovering/resolving (n=2), recovered/resolved (n=58), and unknown (n=1). **POST-MARKETING EXPERIENCE**: A search of the GSDB, as of 12-November-2024, retrieved 1,158 cases with 1,534 events (1,534 serious and 84 non-serious). Characterization of these cases based on source type is presented below. **Post Marketing Study Sources**: Cumulatively, 869 cases with 1,153 events (1,110 serious and 42 non serious) were retrieved from post-marketing study sources. Among these, 869 cases with 1,147 events were retrieved from post-marketing study, 3 cases with 5 events from literature Post Marketing Study and 1 case with 1 event from named patient program (NPP). The most commonly

Important Potential Risk: Overdosing (thrombosis) when Switching to ADYNOVATE from Another FVIII Product or Underdosing (lack of efficacy/bleeding) when Switching from ADYNOVATE to Another FVIII Product	
	reported PTs (≥ 10) were Haemorrhage (n=326), Haemarthrosis (n=315), Drug ineffective (n=74), Contusion (n=66), Muscle haemorrhage (n=43), Epistaxis (n=30), Haematoma (n=22), Mucosal haemorrhage (n=20), Spontaneous haemorrhage (n=19), Mouth haemorrhage (n=13), Gingival bleeding (n=13), Haemorrhage subcutaneous (n=11), Soft tissue haemorrhage (n=10), Traumatic haemorrhage (n=10) and Internal haemorrhage (n=10). The outcome of the events was not recovered/not resolved (n=54), recovering/resolving (n=74), recovered/ resolved with sequelae (n=3), recovered/resolved (n=302), and unknown (n=720). **Spontaneous Sources**: Cumulatively, 338 cases with 466 events (424 serious and 42 non serious) of overdosing (thrombosis) events were retrieved from spontaneous sources. In 1 case with 2 serious events, the suspect product was Helixate Nexgen, and the case is excluded from further analysis. In the remaining 337 cases (464 events), the most commonly reported PTs (≥ 5) were Haemorrhage (n=102), Haemarthrosis (n=101), Muscle haemorrhage (n=31), Factor VIII inhibition (n=24), Drug ineffective (n=20), Contusion (n=15), Epistaxis (n=12), Traumatic haemorrhage (n=10), Haematuria (n=10), Haemorrhage intracranial (n=7), Gastrointestinal haemorrhage (n=6), Cerebral haemorrhage (n=6), Drug half-life reduced (n=5), Haemophilic arthropathy (n=5), Renal haemorrhage (n=5), Anti factor VIII antibody positive (n=5) and Haemorrhage subcutaneous (n=5). The outcome of the events was Fatal (n=8), Not Recovered/Not Resolved (n=17), Recovered/Resolved with Sequelae (n=8), Recovering/ Resolving (n=28), Recovered/ Resolved (n=204), and Unknown (n=199). **Paediatric population**: Cumulatively, in pediatric population 276 cases with 414 events (385 serious and 29 non-serious) were reported. In 1 case with 2 serious events, the suspect product was Helixate Nexgen, and the case is excluded from further analysis. Of the remaining 275 cases with

Important Potential Risk: Overdosing (thrombosis) when Switching to ADYNOVATE from Another FVIII Product or Underdosing (lack of efficacy/bleeding) when Switching from ADYNOVATE to Another FVIII Product	
	412 events, 190 cases (294 events) were retrieved from post-marketing study, 80 cases (112 events) were retrieved from spontaneous sources and 5 cases (6 events) from literature spontaneous sources. The most commonly reported PTs (≥ 7) were Haemorrhage (n=86), Haemarthrosis (n=70), Contusion (n=39), Drug ineffective (n=26), Muscle haemorrhage (n=22), Epistaxis (n=20), Factor VIII inhibition (n=15), Haematoma (n=15), Traumatic haemorrhage (n=9), Spontaneous haemorrhage (n=8), Infusion site haemorrhage (n=8), Mouth haemorrhage (n=7) and Gingival bleeding (n=7). The outcome of the events was not recovered/not resolved (n=25), recovered/resolved with sequelae (n=1), recovering/resolving (n=37), recovered/resolved (n=166), and unknown (n=183). **Geriatric population**: Cumulatively, in geriatric population 52 cases with 93 events (83 serious and 10 non-serious) were reported. Of these 52 cases with 93 events, 21 cases (44 events) were retrieved from post-marketing study sources, 30 cases (47 events) were retrieved from spontaneous sources and 1 case (2 events) from literature spontaneous sources. The most commonly reported PTs (≥ 2) were Haemorrhage (n=12), Haemarthrosis (n=8), Haematoma (n=4), Haemorrhage subcutaneous (n=4), Haemoglobin decreased (n=3), Epistaxis (n=3), Internal haemorrhage (n=2), Haemorrhoidal haemorrhage (n=2), Gastrointestinal haemorrhage (n=2), Melaena (n=2), Injection site haemorrhage (n=2), Muscle haemorrhage (n=2), Intra-abdominal haemorrhage (n=2), Puncture site haemorrhage (n=2), Factor VIII inhibition (n=2), Myocardial infarction (n=2), Traumatic haemorrhage (n=2), Blood urine present (n=2) and Haemophilic arthropathy (n=2). The outcome of the events was fatal (n=4), not recovered/not resolved (n=8), recovering/resolving (n=11), recovered/resolved with sequelae (n=1), recovered/ resolved (n=47), and unknown (n=22). **Pregnant and breast-feeding women**: A search of the GSDB retrieved no cases for pregnant and breast-feeding women.

Important Potential Risk: Overdosing (thrombosis) when Switching to ADYNOVATE from Another FVIII Product or Underdosing (lack of efficacy/bleeding) when Switching from ADYNOVATE to Another FVIII Product	
Risk factors and risk groups:	Patients switching to ADYNOVATE from another FVIII product or patients switching from ADYNOVATE to another product.
Preventability:	Patients should be carefully monitored for lack of efficacy when switching from ADYNOVATE to another FVIII product or increased FVIII levels when switching to ADYNOVATE from another FVIII product.
Impact on the risk-benefit balance of the product:	Patients may experience acute bleeding episodes which, if left untreated, could result in fatal uncontrolled bleeding. Depending on the nature of the thrombotic event, the patient may experience significant disability or death.
Public health impact:	Depending on the severity and nature of the overdosing or underdosing, patients may require medical intervention and costly prolonged hospitalization.

SVII.3.2. Presentation of the missing information

Missing information: Use in Patients ≥65 years of age	
Evidence source:	No clinical data on use in patients ≥65 years of age. **Population in need of further characterisation:** No analyses of an effect of intrinsic factors on PK such as age were conducted during clinical studies. Subjects up to 75 years of age were included in the surgery study (261204) and the continuation study (261302). **Anticipated risk/consequence of the missing information:** While approximately half of new inhibitors (49%) present before the patient is 5 years of age, 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[redacted]. It is not known whether patients 65 years and older would respond differently than younger patients.

Missing information: Use during pregnancy and lactation	
Evidence source:	Pregnant and breast-feeding women were not included in clinical studies with ADYNOVATE. Congenital hemophilia A is an inherited X-chromosome linked recessive bleeding disorder primarily expressed in males. **Population in need of further characterisation:** Safety profile among pregnant and breast-feeding patients. **Anticipated risk/consequence of the missing information:** 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 ADYNOVATE.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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 during pregnancy and lactation

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the following safety concerns

Safety concerns	Specific adverse reaction follow-up questionnaires
Inhibitor formation	Factor VIII Inhibitor Questionnaire Lack of Effect Questionnaire
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)	Central Nervous System (CNS) Questionnaire Renal Questionnaire

Targeted questionnaires are created and implemented to obtain additional information related to a safety concerns (see Annex 4).

Other forms of routine pharmacovigilance activities for the safety concerns:

None.

[redacted]

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Study TAK-660-403
Study short name and title: Evaluation of long-term safety of ADYNOVI/ADYNOVATE (Antihaemophilic Factor [Recombinant] PEGylated, rurioctocog alfa pegol) in patients with haemophilia A – An ADYNOVI/ADYNOVATE Post-Authorisation Safety Study (PASS)
Rationale and study objectives: The main purpose of this study is 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. The primary objective is to assess the long-term safety of prophylaxis with ADYNOVI/ADYNOVATE in patients with haemophilia A in the real-world 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). The secondary objective is 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.
Study design: This Post-Authorisation Safety Study (PASS) is a prospective, multicenter non-interventional clinical study in patients with haemophilia A to monitor the long-term safety of ADYNOVI/ADYNOVATE prescribed prophylactically by their physicians based on their standard clinical practice and in accordance with the product reference information.
Study population: Up to 200 patients with haemophilia A will be enrolled in order to have approximately 100 evaluable patients followed for 5 or more years of prophylaxis treatment (accumulated across all TAK-660 [BAX 855] studies in which each patient participated), and with a minimum of 25 patients followed for 7 years of prophylaxis treatment with ADYNOVI/ADYNOVATE cumulatively. The study will be conducted in Asia, Europe and North America.
Milestones: Interim report: Annual Completion of Study: Final CSR: Q3/Q4 2030

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
TAK-660-403 Ongoing	The main purpose of this study is 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 The primary objective of this study is 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). The secondary objective is 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	- Inhibitor formation - 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 - Thromboembolic events - Hypersensitivity reactions - Overdosing (thrombosis) when switching to ADYNOVATE from another FVIII product or under dosing (lack of efficacy/bleeding) when switching from ADYNOVATE to another FVIII product - Use in patients ≥65 years	Interim Analysis Completion of Study: - Final CSR	Annual Q3/Q4 2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities (by the regulatory authority)				
None				

ADR=Adverse Drug Reaction; AE=Adverse Event; CSR=Clinical study Report; SAE=Serious Adverse Event

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Inhibitor formation	**Routine risk communication:** Sections 4.4, 4.8 in the EU SmPC Sections 2 and 4 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 recommends that all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. SmPC section 4.8 recommends that if such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. **Other routine risk minimisation measures beyond the Product Information:** None proposed
Hypersensitivity reactions	**Routine risk communication:** Sections 4.3, 4.4, and 4.8, in the EU SmPC Sections 2 and 4 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** How to detect early signs of allergic reactions in Sections 2 and 4 of the PL **Other routine risk minimisation measures beyond the Product Information:** None proposed
Thromboembolic events	**Routine risk communication:** None proposed **Routine risk minimisation activities recommending specific clinical measures to address the risk:**

[redacted]

Safety concern	Routine risk minimisation activities
	None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
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)	**Routine risk communication:** Section 5.3 in the EU SmPC **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
Anti-PEG FVIII antibodies	**Routine risk communication:** None proposed **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
Overdosing (thrombosis) when switching to ADYNOVI from another FVIII product or underdosing (lack of efficacy/bleeding) when switching from ADYNOVI to another FVIII product	**Routine risk communication:** None proposed **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
Use in patients ≥ 65 years of age	**Routine risk communication:** Section 5.1 in the EU SmPC **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed

[redacted]

Safety concern	Routine risk minimisation activities
Use during pregnancy and lactation	**Routine risk communication:** Section 4.6 in the EU SmPC Section 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Inhibitor formation	**Routine risk communication:** Sections 4.4, 4.8 in the EU SmPC Sections 2 and 4 of the PL **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Factor VIII Inhibitor Questionnaire • Factor VIII Lack of Effect Questionnaire **Additional pharmacovigilance activities:** PASS TAK-660-403
Hypersensitivity reactions	**Routine risk communication:** Sections 4.3, 4.4, and 4.8 in the EU SmPC Sections 2 and 4 of the PL **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** PASS TAK-660-403

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Thromboembolic events	**Routine risk communication:** None proposed **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** PASS TAK-660-403
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)	**Routine risk communication:** Section 5.3 in the EU SmPC **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Central Nervous System Questionnaire • Renal Events Questionnaire **Additional pharmacovigilance activities:** PASS TAK-660-403
Anti-PEG FVIII antibodies	**Routine risk communication:** None proposed **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** PASS TAK-660-403
Overdosing (thrombosis) when switching to ADYNOVI from another FVIII product or underdosing (lack of efficacy/bleeding) when switching from ADYNOVI to another FVIII product	**Routine risk communication:** None proposed **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** PASS TAK-660-403
Use in patients ≥ 65 years of age	**Routine risk communication:** Section 5.1 in the EU SmPC **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** PASS TAK-660-403

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use during pregnancy and lactation	**Routine risk communication:** Sections 4.4 in the EU SmPC Section 2 of the PL **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004195/human_med_002204.jsp&mid=WC0b01ac058001d124%20

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 during pregnancy and lactation

II.B Summary of important risks

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[redacted]. 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 [redacted].

[redacted]

Important Identified Risk: Inhibitor formation	
	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[redacted]. Approximately half of the new inhibitors (49%) presented before the patient was 5 years of age[redacted]. 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[redacted]. 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) [redacted].
Risk minimisation 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:** 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.

Important Identified Risk: Hypersensitivity	
Risk minimisation 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 pharmacovigilance activities	**Additional pharmacovigilance activities:** 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 [redacted]. 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 minimisation 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 minimisation measures	**Routine risk minimisation measures:** Section 5.3 in the EU SmPC

[redacted]

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)	
	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 minimisation 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: 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 minimisation measures	**Routine risk minimisation measures:** None proposed **Additional risk minimisation measures:** No additional risk minimisation measures.

[redacted]

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	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS TAK-660-403

Missing information: Use in patients > 65 years of age	
Risk minimisation 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 during pregnancy and lactation	
Risk minimisation 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 study is condition 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

None.

[redacted]

PART VII: ANNEXES

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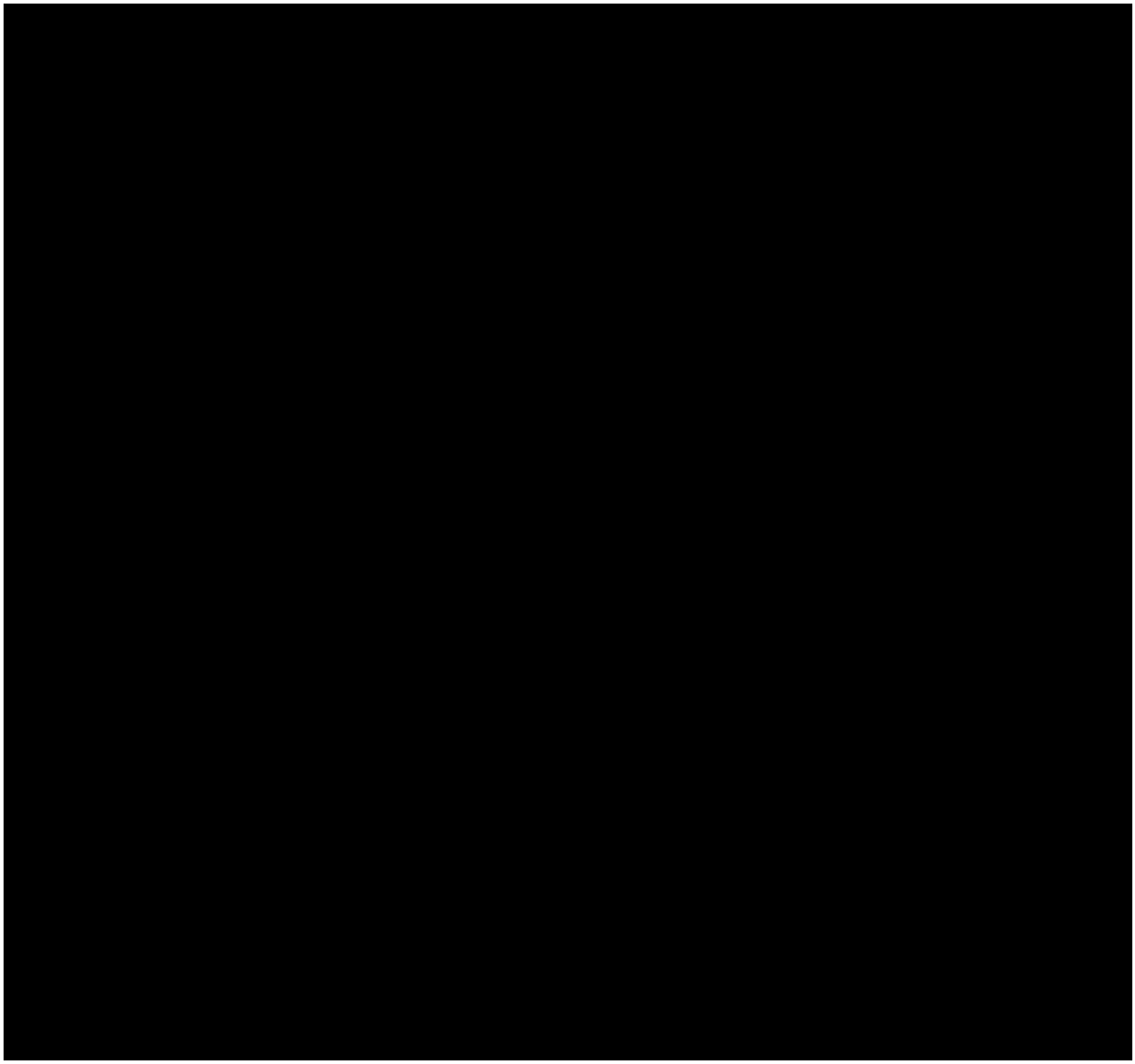
[redacted]

[redacted]

[redacted]



Annex 4: Specific adverse drug reaction follow-up forms

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Factor VIII Inhibitor Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:** **_____**

I. REPORTER INFORMATION		
Name/Title:	Email:	
Postal Address:	Phone:	Fax:
Reporter Type: ☐ Physician ☐ Nurse ☐ Other Health Care Professional		

2. PATIENT INFORMATION		
Patient initials	Gender	Date of Birth or Age
	☐ Male ☐ Female ☐ Not Reported	DOB (ddmmmyyyy) or Age

3. RELEVANT MEDICAL HISTORY / CONCURRENT ILLNESS ☐ **None** ☐ **Unknown** ☐ **Not reported**

Have there been any recent infections? ☐ No ☐ Yes ☐ Unknown ☐ Not reported

If yes, please describe the clinical characteristics and dates over the past year:

Smoker? ☐ Yes ☐ No ☐ Unknown If Yes, state quantity and duration:

Alcohol Use? ☐ Yes ☐ No ☐ Unknown If Yes, state quantity and duration:

Allergies? ☐ Yes ☐ No ☐ Unknown If Yes, list allergies:

Provide Vaccination History if available ☐ Unknown

	Date:
	Date:
	Date:

Age at first exposure:

Is there a family history of hemophilia A?	☐ Yes	☐ No	☐ Unknown	☐ Not Reported
Is there a family history of inhibitor development?	☐ Yes	☐ No	☐ Unknown	☐ Not Reported
Provide FVIII genotype (if known):			☐ Unknown	☐ Not Reported

Severity of Hemophilia A:

☐ Mild (>5% - 40%)

☐ Moderate (1% - 5%)

[redacted]

Factor VIII Inhibitor Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:** **_____**

☐ Severe (<1%) Is there prior inhibitor history ☐Yes ☐ No

Information on last Factor VIII Inhibitor:

FVIII Product received at time of last inhibitor detection:

Max inhibitory level during last episode: BU Date (ddmmmyyyy):

Local lab cut-off for positive inhibitor result: BU Date (ddmmmyyyy):

Did inhibitor resolve? ☐No ☐Yes

Previous Immune Tolerance Induction (ITI) at the time with other product? ☐No ☐Yes If yes, please complete below.

Date Started (ddmmmyyyy):

Regimen:

Exposure days at the time of last inhibitor (approximate) ☐<50 ☐50-150 ☐>150

Comments:

Additional Medical History

Age at first Factor FVIII exposure:

Is there a family history of hemophilia A? ☐ Yes ☐No ☐Unknown ☐Not reported

Is there a family history of inhibitor development? ☐ Yes ☐No ☐Unknown ☐Not reported

Please provide FVIII genotype (if known): ☐Unknown ☐Not reported

Additional relevant inhibitor medical history? ☐ No ☐Yes Please list:

Please include additional medical information in section 3 comments below:

Comments:

4. RELEVANT LAB DATA If not available, indicate ☐ Unknown

Test Name	Date (ddmmmyyyy)	Result	Normal Range
☐HIV serology			
☐HCV serology			
☐HBV			

[redacted]

Factor VIII Inhibitor Questionnaire

Case ID: **Patient/Study ID:**		**Send completed questionnaire by email to [redacted] at:** **_____**	
☐ Lupus Anticoagulant Panel			
☐ aPTT			

Please include additional relevant lab data in comments below.

Comments:

5. SUSPECT PRODUCT INFORMATION ☐ **Unknown** ☐ **Not Reported**

*Suspect Product Name	Indication	**Dose/ Frequency / Route	***Vial Size / Lot number If lot# is unknown provide reason	Number of exposure days if known	Start and Stop Date (ddmmm yyyy)	Check if On-going	****Action taken with product
		Dose: Route: Freq:	Vial: Lot:		Start: Stop:	☐	
		Dose: Route: Freq:	Vial: Lot:		Start: Stop:	☐	
		Dose: Route: Freq:	Vial: Lot:		Start: Stop:	☐	

***Suspect Product Name:** Advate, Adynovate, Hemofil, Immunate, Obizur, Recombinate, If Other Factor VIII product, specify above.

****Total dose of Factor VIII products given:** 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU, 4000 IU, Unknown, Other (specify above)

*****Vial size:** 1 mL prefilled syringe (Obizur only) , 2 mL, 5 mL, 10mL, Unknown, Other (Specify above)

******Action taken with product:** Dose maintained, Dose increased, Dose reduced, Dose reintroduced, Drug

[redacted]

Factor VIII Inhibitor Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:** **_____**
discontinued, Not Applicable, Not reported **Storage Conditions:** ☐Room temperature ☐Refrigerated ☐Frozen ☐Unknown Other storage conditions:	
Please include additional suspect product Information in the section 5 comments below: Section 5 Comments:	
Factor VIII substitution was given for:	☐ Prophylaxis ☐ On Demand ☐ *Surgery ☐ Unknown ☐ Not reported
* If Factor VIII was administered for Surgery, was Factor VIII administered by	☐ Bolus or ☐ Continuous infusion
Current factor VIII therapy administered via:	☐ Bolus ☐ Continuous infusion ☐ Unknown ☐ Not reported

6. FACTOR VIII INHIBITOR INFORMATION

Date (ddmmmyyyy):	**Results**	**Unit of Measurement**
		☐U/dl ☐U/ml ☐%
		☐U/dl ☐U/ml ☐%
		☐U/dl ☐U/ml ☐%

[redacted]

Factor VIII Inhibitor Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:** **_____**

Date of inhibitor detection (ddmmmyyyy): ☐Unknown ☐Not reported

Inhibitor type: ☐ Low titer (≤ 5.0 BU) ☐ High titer (> 5.0 BU) ☐ Unknown

Inhibitor level at first laboratory detection: BU Date (ddmmmyyyy):

Max inhibitor level: BU Date (ddmmmyyyy):

Most recent inhibitor level: BU Date (ddmmmyyyy):

Local lab cut-off for positive inhibitor result: BU Date (ddmmmyyyy):

Assay Type?

Was inhibitor eradicated? ☐No ☐Yes (If yes, please provide Date (ddmmmyyyy):

Did the inhibitor involve any of the following? ☐No ☐Yes

If Yes, please specify:

☐Hospitalization from (ddmmmyyyy) to ddmmmyyyy)

☐Medically Significant ☐Life-Threatening ☐Disability ☐Death

Death of (ddmmmyyyy): Cause(s):

Is the Factor VIII inhibitor related to treatment with the [redacted] product? ☐No ☐Yes ☐Unknown

Has the patient recovered? ☐Recovered on (ddmmmyyyy) ☐Recovered with Sequelae ☐

Recovering ☐Fatal ☐Not recovered ☐Unknown ☐Not reported

7. TREATMENT GIVEN for INHIBITOR?

☐ **Yes, complete below** ☐**None** ☐**Unknown** ☐**Not Reported**

Drug Name / Name of Non-Drug Name	Dose / Frequency / Route of Administration	Start Date (ddmmmyyyy)	Stop Date (ddmmmyyyy)	Check if On-going
	Dose : Route: Freq:			☐
	Dose : Route:			☐

[redacted]

Factor VIII Inhibitor Questionnaire

Case ID: **Patient/Study ID:**		**Send completed questionnaire by email to [redacted] at:** **_____**		
	Freq:			
	Dose : Route: Freq:			☐

Did the inhibitor involve any of the following? ☐No ☐Yes

If Yes, please specify:

☐Death on (ddmmmyyyy): Cause(s):

☐Hospitalization from (ddmmmyyyy) to ddmmmyyyy)

☐Medically Significant ☐Life-Threatening ☐Disability

Is the Factor VIII inhibitor related to treatment with the [redacted] product? ☐No ☐Yes ☐Unknown

Outcome: ☐Recovered on (ddmmmyyyy) ☐Recovered with Sequelae ☐Recovering ☐Not recovered ☐Unknown / Not reported, ☐ Fatal (include date ddmmmyyyy):

Please include additional treatment Information in Section 8 below.

Section 8 Comments:

SECTION 8: INFORMATION ON IMMUNE TOLERANCE INDUCTION (ITI)

Was immune tolerance induction (ITI) initiated? ☐No ☐Yes ☐Unknown ☐Not reported

(If yes, please answer below)

Date Started (ddmmmyyyy): End Date (ddmmmyyyy): ☐ Ongoing

Regimen:

Inhibitor level at start of ITI: BU Date (ddmmmyyyy):

Maximum titer during ITI: BU Date (ddmmmyyyy):

Last inhibitor titer tested during ITI: BU Date (ddmmmyyyy):

Is the patient participating in an ITI trial? ☐No ☐Yes

If yes, please provide name of study:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:** **_____**

9. ADDITIONAL INFORMATION

QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

[redacted]

Lack of Effect Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:**

I. REPORTER INFORMATION

Name/Title:	Email:	
Postal Address:	Phone:	Fax:

Reporter Type: ☐ Physician ☐ Nurse ☐ Other Health Care Professional

2. PATIENT INFORMATION

Patient Initials:	Gender	Date of Birth or Age
	☐Female ☐Male ☐Not Reported	DOB (ddmmmyyyy): or Age:

3. RELEVANT MEDICAL HISTORY / CONCURRENT ILLNESS ☐None ☐Unknown ☐Not reported

Have there been any recent infections? ☐No ☐Yes ☐ Unknown ☐Not reported

If yes, please describe the clinical characteristics and dates over the past year:

Risk Factors:

Smoker? ☐Yes ☐No ☐Unknown If Yes, state quantity and for how long:

Alcohol Use? ☐Yes ☐No ☐Unknown If Yes, state quantity and for how long:

Allergies? ☐Yes ☐No ☐Unknown If Yes, list allergies:

Please include additional Relevant Medical History in Section 3 Comments below.

Provide vaccination history if available	☐ Unknown
	Date:
	Date:
	Date:

Age of first exposure: Is there a family history of hemophilia A? ☐Yes ☐No ☐ Unknown ☐Not Reported

Is there a family history of inhibitor development? ☐Yes ☐No ☐Unknown ☐Not Reported

Provide FVIII genotype if known: ☐Unknown ☐Not Reported

List additional relevant inhibitory medical history:

Severity of	**Coagulation Factor VIII**	**Bleeding Episodes:**

[redacted]

Lack of Effect Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:**

Hemophilia	**Levels at start of bleeding:**	
☐ Mild (>5% - 40%) ☐ Moderate (1% - 5%) ☐ Severe (<1%)		What were the circumstances of lack of effect (e.g., surgery, breakthrough bleed, other, specify)? How many bleeding episodes does the patient have per year?
Is there a prior inhibitor history: ☐Yes ☐No		

Factor VIII Inhibitor:

Has the patient ever had a Factor VIII inhibitor? ☐Yes ☐No ☐Unknown ☐ Not tested ☐ Results pending

Inhibitor Type: ☐Low titer (≤ 5.0 BU) ☐High titer (> 5.0) ☐Unknown

What was the most recent inhibitor test result? BU Date of Test (ddmmmyyyy):

What FVIII Product was received when the inhibitor developed?

How was the inhibitor treated, if known:

Previous Product:

Has the patient switched Factor VIII product in the last 12 months?	☐Yes ☐No ☐Unknown

If YES, please complete the information below about the previous product.

Product – Including Concentration	Lot #	Dose / Frequency	Start Date (ddmmmyyyy)	Date of Product Switch (ddmmmyyyy)	Reason for Product Switch
		Dose: Freq:			
		Dose: Freq:			
		Dose: Freq:			

Was FVIII inhibitor formation identified with the previous product?	☐Yes ☐No ☐ Unknown

Please include additional Relevant Medical History below.

Comments:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:**

4. RELEVANT LAB DATA ☐ Unknown ☐ Not Reported

Test Name	Date (ddmmmyyyy)	Result	Normal Range
HIV serology			
HCV serology			
HBV			
Lupus Anticoagulant Panel			
aPTT			

Please include additional Relevant Lab Data below.

Section 4 Comments:

5. SUSPECT PRODUCT INFORMATION ☐ Unknown ☐ Not Reported

*Suspect Product Name	**Vial Size / Lot# If Lot number unknown, provide reason	***Dose/ Frequency / Route of Admin	Indication	Number of exposure days if known	Start and Stop Date (ddmmm yyyy)	Check if On-going	****Action taken with product
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	

[redacted]

Lack of Effect Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:**

	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	

***Suspect Product Name:** Advate, Adynovate, Hemofil, Immunate, Obizur, Recombinate, If Other, specify above.

****Vial size:** 1 mL prefilled syringe (Obizur only), 2 mL, 5 mL, 10mL, Unknown

*****Total dose of Factor VIII products given:** 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU, 4000 IU, Unknown, If Other, specify above.

******Action taken with product:** Dose maintained, Dose increased, Dose reduced, Dose reintroduced, Drug discontinued,
Not Applicable, Not reported

Storage Conditions: ☐Room temperature ☐Refrigerated ☐Frozen ☐Unknown Other storage conditions:

Treatment Regimen:

☐ Prophylaxis ☐ On Demand ☐*Surgery ☐Unknown ☐Not Reported

*If Factor VIII was administered for surgery by: ☐ Bolus or ☐ Continuous Infusion

Prophylaxis (answer the following if on Prophylaxis therapy):

What was the number of breakthrough bleeds in the last 6 months during prophylaxis treatment?

Are there more frequent bleeds now? ☐Yes ☐No ☐Unknown

If YES, what is the increase in the number of bleeds in the last 6 months?

Are the bleeds more severe now? ☐Yes ☐No ☐Unknown

Are the bleeds more difficult to control? ☐Yes ☐No ☐Unknown

Does the patient require an increased dose compared to the usual dose? ☐Yes ☐No ☐ Unknown

If YES, what is the increase in the patient's dose?

Does the patient require more than the expected number of infusions? ☐Yes ☐No ☐Unknown

If YES, what is the total number of infusions required to stop the bleed?

Has the patient missed any doses from the prescribed dose schedule? ☐Yes ☐No ☐Unknown

If YES, please describe:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:**

On Demand (answer the following if On Demand therapy):

For the event, does the patient require an increased dose compared to the usual dose? ☐Yes ☐ No ☐Unknown

If YES, what is the increase in the patient's dose?

Does the patient require more than the expected number of infusions? ☐Yes ☐No ☐Unknown

If YES, what is the total number of infusions required to stop the bleed?

Total Dose given (IU/kg) to stop the bleed?

Please include additional Suspect Product Information below.

Section 5 Comments:

6. FACTOR VIII LACK OF EFFECT INFORMATION

Date of Diagnosis (ddmmmyyyy): ☐ Unknown / Not reported

Clinical Symptoms Associated with the Lack of Effect:

Event	Onset date **(ddmmmyyyy)**	End Date **(ddmmmyyyy)**	Check if Ongoing
			☐
			☐
			☐
			☐

Was the Lack of Effect considered serious? ☐Yes ☐No ☐Unknown

If YES, please specify:

☐Hospitalization from (ddmmmyyyy) to (ddmmmyyyy)

☐Medically Significant ☐Life-Threatening ☐Congenital Anomaly ☐Disability

☐Death on (ddmmmyyyy) Cause(s) of death:

Is the lack of effect related to treatment with [redacted] product? ☐Yes ☐No ☐Unknown

Outcome:

☐Recovered on (ddmmmyyyy): ☐Recovered with Sequelae ☐Recovering ☐Not recovered ☐ Unknown ☐Not Reported

☐Fatal, include date (ddmmmyyyy)

Has the patient experienced any of the following situations?

[redacted]

Lack of Effect Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:**

Increase in physical activity level? ☐Yes ☐No ☐Unknown

If YES, describe Changes in activity (e.g., sports):

Increase or decrease in weight? ☐Yes ☐No ☐Unknown

If YES, describe changes in weight:

Any recent surgery or hospitalization that required increase in dosing? ☐Yes ☐No ☐Unknown

If YES, describe events:

Based on the above facts:

Has the dose been changed? ☐Yes ☐No ☐Unknown

If YES, what is the current dose and when was it started:

As a result of the adverse event, were any pharmacokinetic investigational tests done? ☐Yes ☐No ☐Unknown

If YES, please provide the results:

Please include additional Lack of Effect information below (e.g., site and severity of bleed).

Section 7 Comments:

7. TREATMENT GIVEN FOR LACK OF EFFECT: ☐ No treatment given ☐Not Reported

Drug Name/Name of Non-Drug Therapy	Dose / Frequency / Route of Administration (if applicable)	Start and Stop Date (ddmmmyyyy)	Check if Ongoing
	Dose: Route: Freq:	Start: Stop:	☐
	Dose: Route: Freq:	Start: Stop:	☐
	Dose: Route: Freq:	Start: Stop:	☐

Please include additional Treatment information below.

Section 8 Comments:

8. ADDITIONAL INFORMATION

[redacted]

Lack of Effect Questionnaire

Case ID: **Patient/Study ID:**		**Send completed questionnaire by email to [redacted] at:**
QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at: _____**

I. REPORTER INFORMATION

Name/Title:	Email:	
Postal Address:	Phone:	Fax:
Reporter Type: ☐ Physician ☐ Nurse ☐ Other Health Care Professional		

Reported Verbatim Neurological Event(s)

Symptom	**Latency** (Time from first use of suspected product to onset of symptom)	**Severity** M= Mild; D= Moderate; S= Severe If yes, describe.	**Onset Date** (ddmmmyyyy)	**End Date** (ddmmmyyyy)	**Check if Ongoing**
					☐
					☐

Other Neurological Signs and Symptoms (check all that apply)

Symptom	**Latency** (Time from first use of suspected product to onset of symptom)	**Severity** M= Mild; D= Moderate; S= Severe If yes, describe.	**Onset Date** (ddmmmyyyy)	**End Date** (ddmmmyyyy)	**Check if Ongoing**
☐ Lethargy					☐
☐ Fatigue					☐
☐ Hyperactivity					☐
☐ Restlessness					☐
☐ Insomnia					☐
☐ Confusion					☐

[redacted]

Case ID: **Patient/Study ID:**			**Send completed questionnaire by email to [redacted] at: _____**		
☐ Poor physical coordination					☐
☐ Slurred speech					☐
☐ Anxiety					☐
☐ Dizziness / lightheadedness					☐
☐ Seizures					☐
☐ Learning disability					☐
☐ Impaired cerebrospinal circulation					☐
☐ Depression					☐
☐ Loss of consciousness					☐
☐ Mood swings					☐

2. DIAGNOSTIC TESTS If checked, provide results	
☐ Spinal tap	
☐ MRI	
☐ CT	
☐ Lumbar puncture	
☐ Positive emission tomography	
☐ Electroencephalogram	
☐ Electromyography	
☐ Lead level	
Other diagnostic details	

3. PATIENT INFORMATION		
Patient Initials	Gender	Date of Birth or Age
	☐ Male ☐ Female ☐ Not Reported	DOB (ddmmmyyyy): or Age:

4. BACKGROUND PEG (POLYETHYLENE GLYCOL) EXPOSURE (the reporter is encouraged to check labeling ingredients for various products to complete this section):	
PEG containing exposure	**Product used, and Dates of exposure and additional details**

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at: _____**
Skin creams, moisturizers, lotions, emollients used	
Toothpaste	
Laxatives (GoLYTELY, GlycoLax, Fortrans, TriLyte, Colyte, Halflytely, Macrogol, MiraLAX, MoviPrep)	
Prescription medications containing PEG	
Foods containing PEG (processed foods may use PEG as anti-foaming agent)	

5. INFORMATION ON HEMOPHILIA TREATMENT PRODUCT(S): ☐ **Unknown** ☐ **Not Reported**

*Suspect Product Name	**Vial Size/ Lot # If lot # unknown, provide reason	***Dose Frequency / Route of Admin	Indication(s)	Number of exposure days if known	Start and Stop Date (ddmmm yyyy)	Check if Ongoing	****Action taken with product
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	

[redacted]

Case ID: **Patient/Study ID:**				**Send completed questionnaire by email to[redacted] at: _____**			
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	

***Suspect Product Name:** Advate, Adynovate, Hemofil, Immunate, Feiba, Obizur, Recombinate,

If Other Factor VIII product, specify above.

****Vial size:** 1 mL prefilled syringe (Obizur only) , 2 mL, 5 mL, 10mL, Unknown, Other (specify above)

*****Total dose of Factor VIII products given:** 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 1700 IU (Feiba only), 2000 IU, 3000 IU, 4000 IU, Unknown, Other (specify above)

******Action taken with product:** Dose maintained, Dose increased, Dose reduced, Dose reintroduced, Drug discontinued,

Not Applicable, Not reported

Storage Conditions: ☐Room temperature ☐Refrigerated ☐Frozen ☐Unknown Other storage conditions:

Include additional comments on Product information below.

Comments:

6. ADDITIONAL INFORMATION

QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at:** _____

I. REPORTER INFORMATION

Name/Title:	Email:	
Postal Address:	Phone:	Fax:
Reporter Type: ☐ Physician ☐ Nurse ☐ Other Health Care Professional		

Reported Verbatim Renal Event(s)

Symptom	**Latency** (Time from first use of suspected product to onset of symptom)	**Severity** M= Mild; D= Moderate; S= Severe If yes, describe.	**Onset Date** (ddmmmyyyy)	**End Date** (ddmmmyyyy)	**Check if Ongoing**
					☐
					☐

Other Renal Signs and Symptoms associated with this event (check all that apply)

Symptom	**Latency** (Time from first use of suspected product to onset of symptom)	**Severity** M= Mild; D= Moderate; S= Severe If yes, describe.	**Onset Date** (ddmmmyyyy)	**End Date** (ddmmmyyyy)	**Check if Ongoing**
☐Painful urination					☐
☐Foamy urine					☐
☐Frequent urination					☐
☐Blood in urine					☐
☐Unspecified urinary problems (please specify in comment section below)					☐
☐Kidney infection					☐
☐Difficulty emptying bladder					☐
☐Swelling / inflammation of the kidneys					☐
☐Peripheral swelling					☐

Additional Comments:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at: _____**

2. DIAGNOSTIC TESTS, If checked, provide results

Name of Test	Test Result	Date of Test (ddmmmyyyy)	Normal Reference	Date resolved (ddmmmyyyy)	Check if Ongoing
☐Serum Creatinine					
☐Blood urea nitrogen					
☐Creatinine clearance					
☐Urine creatinine					
☐Urinalysis					
☐GFR					
☐Renal Ultrasound					
☐CT of Kidneys					
☐Renal biopsy, If yes provide results					

3. PATIENT INFORMATION

Patient Initials	Gender	Date of Birth or Age
	☐Male ☐Female ☐ Not Reported	DOB (ddmmmyyyy) or Age:

4. BACKGROUND PEG (POLYETHYLENE GLYCOL) EXPOSURE (the reporter is encouraged to check labeling ingredients for various products to complete this section):

PEG containing exposure	**Product used, and Dates of exposure and additional details**
Skin creams, moisturizers, lotions, emollients used	
Vaccine	
Toothpaste	
Laxatives (GoLYTELY, GlycoLax, Fortrans, TriLyte, Colyte, Halflytely, Macrogol, MiraLAX, MoviPrep)	
Prescription medications containing PEG	
Foods containing PEG (processed foods may use PEG as anti-foaming agent)	

5. RELEVANT MEDICAL/FAMILY HISTORY/ CONCURRENT ILLNESS ☐ Unknown ☐ Not Reported

Please check history or family history of the following (if not specified above):

☐Congenital kidney problems	☐Kidney stones	☐Family history of kidney disease	☐Hemodialysis

[redacted]

Case ID: **Patient/Study ID:**		**Send completed questionnaire by email to [redacted] at:** _____	
☐Kidney failure	☐Radiation to abdomen or pelvis	☐Chemotherapy for cancer	☐Peritoneal dialysis
Other kidney problems, please specify:			
Include additional medical / family history comments (describe if any of the above were checked below).			
Comments:			

6. INFORMATION ON HEMOPHILIA TREATMENT PRODUCT(S): ☐ **Unknown** ☐ **Not Reported**

*Suspect Product Name	**Vial Size Lot # If lot # unknown, provide reason	***Dose Frequency / Route of Admin	Indication(s)	Number of exposure days if known	Start and Stop Date (ddmmm yyyy)	Check if Ongoing	****Action taken with product
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	
	Vial: Lot:	Dose: Route: Freq:			Start: Stop:	☐	

***Suspect Product Name:** Advate, Adynovate, Hemofil, Immunate, Feiba, Obizur, Recombinate, If Other Factor VIII product, specify above.

****Vial size:** 1 mL prefilled syringe (Obizur only), 2 mL, 5 mL, 10mL, Unknown, Other (specify above)

*****Total dose of Factor VIII products given:** 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 1700 IU (Feiba only), 2000 IU, 3000 IU, 4000 IU, Unknown, Other (specify above)

******Action taken with product:** Dose maintained, Dose increased, Dose reduced, Dose reintroduced, Drug discontinued, Not Applicable, Not reported

Storage Conditions: ☐Room temperature ☐Refrigerated ☐Frozen ☐Unknown Other storage conditions:

Include additional comments on Product information below.

Comments:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to [redacted] at: _____**

7. ADDITIONAL INFORMATION

QUESTIONNAIRE COMPLETED BY	Printed Name:		Today's Date:
	Signature:		
	Address:		
	Contact Number:	Email:	

[redacted]

[redacted]

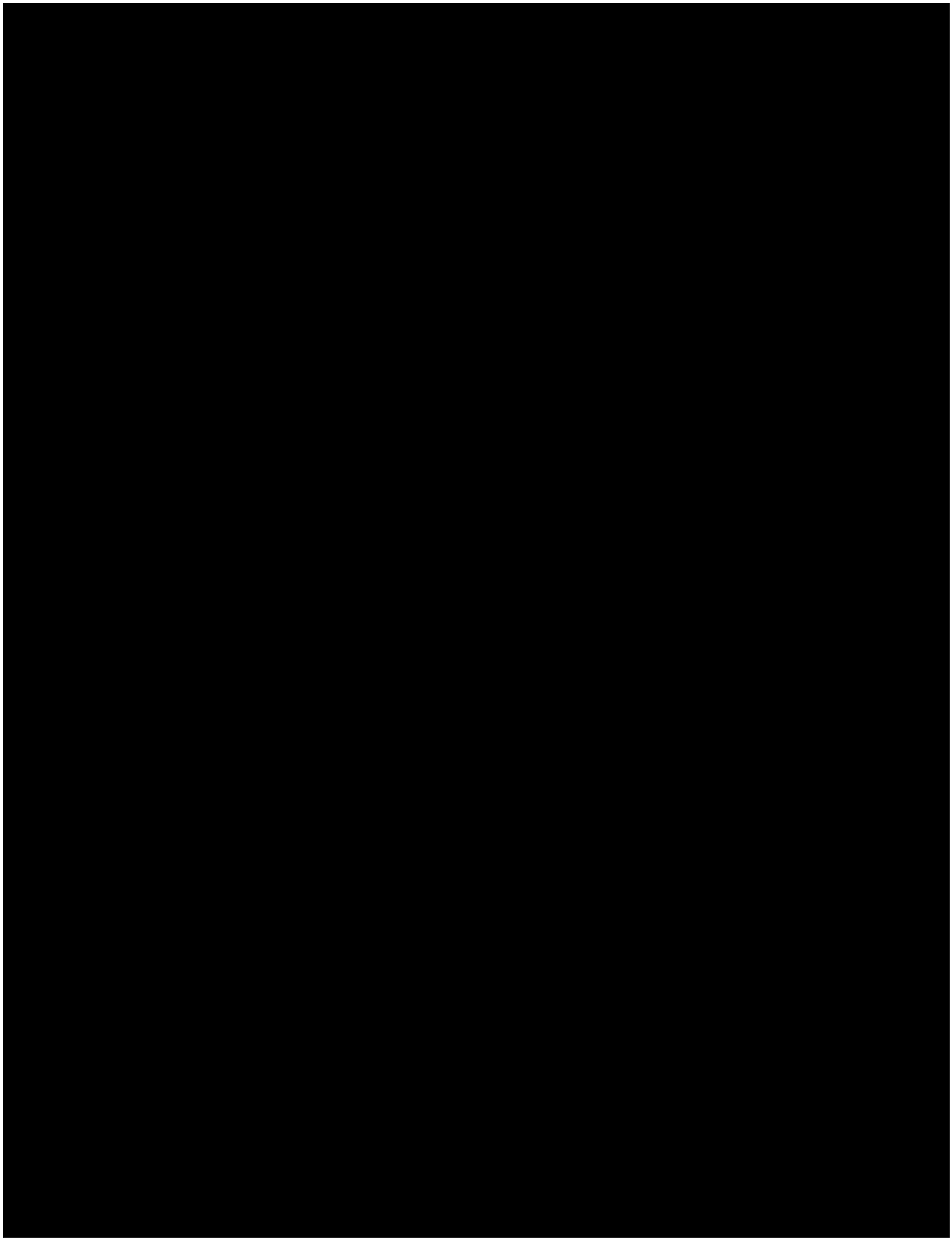
Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable

[redacted]

[redacted]

[redacted]



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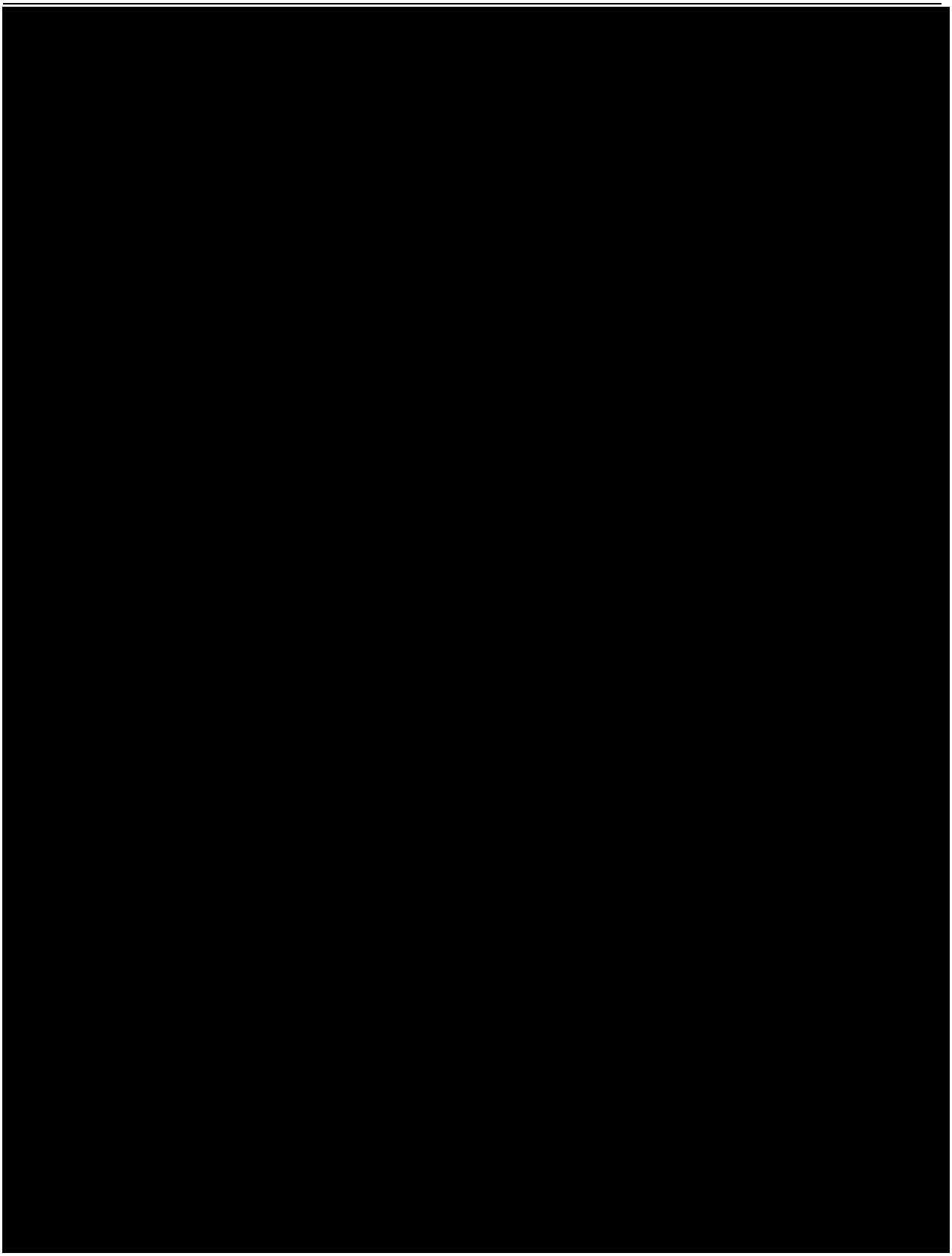

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