Summary of risk management plan for Esperoct

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

The Summary of Product Characteristics (SmPC) of Esperoct and its package leaflet give essential information to healthcare professionals and patients on how Esperoct should be used.

This summary of the RMP for Esperoct 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 EPAR.

Important new concerns or changes to the current ones will be included in the RMP updates for Esperoct.

I. The medicine and what it is used for

Esperoct is authorised for treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency). It contains turoctocog alfa pegol as the active substance and it is given by intravenous route.

Further information about the evaluation of benefits of Esperoct can be found in the EPAR for Esperoct, including in its plain-language summary, available on the EMA website, under the medicine's webpage: EPAR link

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

Important risks of Esperoct, together with measures to minimise such risks and the studies for learning more about the risks of Esperoct, 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 public (e.g., with or without prescription) can help to minimises its risks.

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

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

II.A List of important risks and missing information

Important risks of Esperoct 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 Esperoct. 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). An overview of important risks and missing information for Esperoct is provided below.

List of important risks and missing information	
Important identified risks	• Inhibitor development • Allergic/hypersensitivity reactions
Important potential risks	• Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs • Anti-PEG antibodies • Thromboembolic events
Missing information	• Use in pregnant and lactating women

Abbreviations: FVIII = factor VIII; PEG = polyethylene glycol.

II.B Summary of important risks

An overview of important identified risks, important potential risks and missing information for Esperoct is provided in the tables below.

Important identified and important potential risks

Important identified risks	
Inhibitor development	
Evidence for linking the risk to the medicine	Theoretical considerations, literature and experience from marketed FVIII products on the market.
Risk factors and risk groups	The risk of inhibitor development is the highest in PUPs. In PUPs, the risk of developing inhibitors is highest within the first 20 exposure days. Several patient-related factors have been associated with the risk of developing inhibitors, such as FVIII gene mutation, other genetic factors, family history of inhibitors and ethnicity. Non-genetic risk factors include vaccinations, surgery and intensive treatment.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: The identified risk of developing Inhibitors to FVIII is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for careful monitoring by appropriate clinical observations and laboratory tests is included in SmPC Section 4.4 and PL Section 2. Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS (NN7088-4029) PASS; Non-interventional registry study (NN7088-4557) See Section II.C of this summary for an overview of the post-authorisation development plan.

Allergic/hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trials, literature and experience from marketed FVIII products.
Risk factors and risk groups	Patients with a history of allergic reactions or with known hypersensitivity to the active substance (rFVIII or PEG), to Chinese hamster proteins or to excipients are at higher risk. The risk of allergic/hypersensitivity reactions is expected to be higher with the initial administrations compared to subsequent administrations.
Risk minimisation measures	Routine risk minimisation measures: <u>Routine risk communication</u>: The identified risk of allergic/hypersensitivity reactions is addressed in the labelling: Sections 4.8 of the SmPC and Section 4 of the PL. Hypersensitivity to the active substance or excipients and known allergy to hamster protein are listed as contraindication in Section 4.3 of SmPC and Section 2 of PL. <u>Risk minimisation activities in the Product Information beyond routine risk communication</u>: Information on how to detect early signs of allergic/hypersensitivity reactions is included in SmPC Section 4.4 of SmPC and Section 2 of PL. <u>Other routine risk minimisation measures beyond the Product Information</u>: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS (NN7088-4029) PASS; Non-interventional registry study (NN7088-4557) See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risks	
Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs	
Evidence for linking the risk to the medicine	Theoretical considerations based on literature. There has been no indication of PEG accumulation after N8-GP treatment nonclinical or clinically. In the N8-GP chronic repeat dose toxicity studies in Rowett Nude Rats, no treatment-related histopathological changes or signs of PEG accumulation were seen in any organs. PEG was not detected in any brain tissues (including the choroid plexus) by a PEG-specific immunohistochemistry staining. Single-dose metabolism and excretion studies were performed in rats, with N8-GP radiolabelled in the PEG moiety. The excretion study showed that N8-GP/40 kDa PEG is excreted in urine and faeces. The distribution study in rats showed that PEG is gradually eliminated from all organs over time; terminal elimination of PEG was estimated in all tissues in the rat and ranged from 14 days (plasma) to 89 days (choroid plexus). This indicates that PEG concentrations will not continue to accumulate

	indefinitely but will reach steady state concentrations in plasma and tissues. When assessing the clinical relevance of the data from the rat distribution study, applying allometric scaling predicts time to reach steady-state PEG levels in human tissues to 1–3 years, indicating that steady-state PEG concentrations have been reached in all organs in the N8-GP clinical development programme. At the cut-off date for this RMP[a] the clinical development programme supports more than 5 years exposure of N8-GP. Clinical safety data available for other relevant marketed pegylated products containing ≥40 kDa PEG have not shown any clinically relevant adverse reactions associated with PEG accumulation.
Risk factors and risk groups	Currently, there are no known risk factors for accumulation of PEG in the brain and in other tissues/organs after long-term treatment with N8-GP.
Risk minimisation measures	Routine risk minimisation measures: <u>Routine risk communication</u>: None <u>Risk minimisation activities in the Product Information beyond routine risk communication</u>: None <u>Other routine risk minimisation measures beyond the Product Information</u>: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS (NN7088-4029) PASS; Non-interventional registry study (NN7088-4557) See Section II.C of this summary for an overview of the post-authorisation development plan.
Anti-PEG antibodies	
Evidence for linking the risk to the medicine	The risk was based on literature, labelling of others pegylated products and post-marketing data for N8-GP.
Risk factors and risk groups	No specific risk factors are known for the development of anti-PEG antibodies with the use of N8-GP. Moreover, the heterogeneity of the cases reported as of the DLP of this report does not allow the MAH to specify a particular patient population to be at risk.
Risk minimisation measures	Routine risk minimisation measures: <u>Routine risk communication</u>: The risk of previously treated patients experiencing decreased FVIII activity, in the absence of detectable FVIII inhibitors is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. <u>Risk minimisation activities in the Product Information beyond routine risk communication</u>:

	Recommendation for careful monitoring by appropriate clinical observations and laboratory tests is included in SmPC Section 4.4 and PL Section 2. Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None
Thromboembolic events	
Evidence for linking the risk to the medicine	Theoretical considerations, literature and experience from marketed FVIII products.
Risk factors and risk groups	Possible general risk factors (not specific for patients with haemophilia A only) include thromboembolic diseases, disseminated intravascular coagulation, liver disease, advanced atherosclerotic disease, arrhythmias, hypertension, crush injury, cancer, diabetes, hypercholesterolaemia, obesity, post-surgical status, septicaemia, immobilisation, smoking, old age, new-born infants and use of central venous access devices.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: None Risk minimisation activities in the Product Information beyond routine risk communication: None Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

[a]13 Oct 2021.

Abbreviations: FVIII = factor VIII; PASS = post-authorisation safety study; PEG = polyethylene glycol; PL = package leaflet; PUP = previously untreated patient; rFVIII = recombinant factor VIII; RMP = risk management plan; SmPC = Summary of Product Characteristics.

Missing information

Use in pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: Lack of experience in this population is mentioned in Section 4.6 of the SmPC. Risk minimisation activities in the Product Information beyond routine risk communication: None Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Abbreviations: SmPC = Summary of Product Characteristics.

II.C Post-authorisation development plan

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

The following study is a condition of the marketing authorisation:

Turoctocog alfa pegol (N8-GP) Non-interventional Post-authorisation Safety Study (PASS; NN7088-4029)

Purpose of the study: The main purpose of this prospective, multinational, non-interventional post-authorisation study is to evaluate the long-term safety of turoctocog alfa in patients with haemophilia A receiving prophylactic treatment and possible clinical consequences hereof under observational (‘real world’) conditions of routine clinical care.

Primary objective

The primary objective of the study is to investigate the long-term safety of turoctocog alfa pegol including the PEG moiety of the substance during routine prophylaxis in patients with haemophilia A.

Secondary objectives

Secondary objectives are to further evaluate the general safety including FVIII inhibitors and allergic/hypersensitivity reactions of N8-GP during routine use in patients with haemophilia A under the circumstances it was prescribed.

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

Non-interventional registry study (NN7088-4557)

Purpose of the study: The main purpose of this registry based, non-interventional PASS is to evaluate the longer-term safety of turoctocog alfa pegol in patients with haemophilia A and possible clinical consequences under observational ('real world') conditions of routine clinical care.

Primary objective

The primary objective of this registry-based non-interventional study is the investigation of long term safety of turoctocog alfa pegol including the PEG moiety of the substance during routine prophylaxis in patients with haemophilia A as prescribed by healthcare professionals. Data will derive from third party data obtained through European registry public health surveillance initiatives of haemophilia patients (EUHASS).

Secondary objective

To assess specific pharmacological risks for FVIII replacement products (FVIII inhibitors, allergic type hypersensitivity reactions).