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Summary of risk management plan for Alprolix (eftrenonacog alfa)

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

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

This summary of the RMP for Alprolix 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 Alprolix's RMP.

I. The medicine and what it is used for

Alprolix is authorised for treatment and prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency). Alprolix can be used for all age groups (see SmPC for the full indication). It contains eftrenonacog alfa (recombinant coagulation factor IX Fc fusion protein) as the active substance and it is given by intravenous injection.

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

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

Important risks of Alprolix, together with measures to minimise such risks and the proposed studies for learning more about Alprolix's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In 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 Alprolix is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Alprolix are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Alprolix. 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 development to factor IX Serious hypersensitivity
Important potential risks	Serious vascular thromboembolic events
Missing information	None

II.B Summary of important risks

Important identified risk: Inhibitor development to factor IX	
Evidence for linking the risk to the medicine	This is a known risk for factor IX replacement therapy, including Alprolix. Inhibitor development have been observed in the completed study in previously untreated patients (Study 998HB303) and in the postmarketing setting.
Risk factors and risk groups	The causes of inhibitor development to factor IX are not known. Hemophilia B patients are at highest risk of inhibitor development to factor IX during the first 50 exposure days. Mutations in the factor 9 gene that confer the highest risk of inhibitor formation are large or gross gene deletions, which account for less than one quarter of hemophilia B patients. Robust data on risk factors specific for factor IX inhibitors are lacking.
Risk minimisation measures	**Routine risk communication**: SmPC section 4.8. PL section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for monitoring development of inhibitors by appropriate clinical observation and laboratory tests are included in SmPC section 4.4 How to detect early signs and symptoms of inhibitor development in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	European Haemophilia Safety Surveillance System (EUHASS) and European Pediatric Network (PedNet) registry participation and data collection. See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Serious hypersensitivity	
Evidence for linking the risk to the medicine	This is a known risk for factor IX replacement therapy, including Alprolix. Serious hypersensitivity reactions considered to be related to Alprolix have been observed in the completed study in previously untreated patients in the setting of factor IX inhibitor (Study 998HB303) and postmarketing setting. Anaphylaxis related to Alprolix has been observed in the postmarketing setting.
Risk factors and risk groups	Allergic reactions in hemophilia B patients often occur prior to or concomitant with inhibitor formation. The occurrence tends to be associated with young age, few exposure days, and a high-risk genotype.
Risk minimisation measures	Routine risk communication: SmPC section 4.8. PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Hypersensitivity to the active substance or excipients is a contraindication, SmPC section 4.3 Recommendation to immediately discontinue use of product and contact their physician if symptoms of hypersensitivity occur are included in SmPC sections 4.4 Instruction to not use product if allergic to active substance or any other ingredients in PL Section 2. How to detect and handle early signs and symptoms of allergic reactions and anaphylaxis in PL section 2. Other routine risk minimisation measures beyond the Product Information: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	European Haemophilia Safety Surveillance System (EUHASS) and European Pediatric Network (PedNet) registry participation and data collection. See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Serious vascular thromboembolic events	
Evidence for linking the risk to the medicine	Elevated levels of factor IX have been associated with a risk of deep vein thrombosis in the non-hemophilia population and there is a potential risk of thromboembolic episodes following the administration of factor IX products. The overall incidence of thromboembolic events associated with the use of recombinant factor IX, such as Alprolix, has not been established. Case reports of venous thrombosis in hemophilia patients in the presence of surgery have been published; however, the incidence remains unclear.
Risk factors and risk groups	Surgery, continuous infusion, and use of activated prothrombin complex concentrates and plasma derived factor IX were identified from case reports as risk factors for thromboembolic events in hemophilia B patients.
Risk minimisation measures	**Routine risk communication:** SmPC section 4.8. PL section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Information about risk of thrombotic complications are included in SmPC section 4.4 Information about risk of cardiovascular events in patient with existing cardiovascular risk factors is included in SmPC section 4.4 Information about risk of catheter-related complications, including catheter site thrombosis is included in SmPC section 4.4 Information about risk of risk of blood clots and catheter-related complications, including catheter site thrombosis is described in PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	European Haemophilia Safety Surveillance System (EUHASS) participation and data collection. See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Alprolix.

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

- Data collection from participation in the European Haemophilia Safety Surveillance System (EUHASS) registry.

Purpose of the study: To monitor the treatment safety of hemophilia B.

- Data collection from participation in the European Pediatric Network (PedNet) registry.
  Purpose of the study: To monitor the treatment safety of hemophilia B.