CSL Behring

Afstyla

Recombinant SingleChain Factor VIII (rVIII-SingleChain) / Lonoctocog alfa

Swiss Summary of Risk Management Plan

Version number of RMP: 5.0

Marketing Authorization Holder: CSL Behring Lengnau AG

Date: 25-Feb-2020

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.
The RMP summary of Afstyla is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Afstyla in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. CSL Behring AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Afstyla.

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The medicine and what it is used for

Afstyla, Recombinant Single-Chain Factor VIII (rVIII-SingleChain), is a type of FVIII replacement therapy and is authorized for treatment and prevention of bleeding episodes in patients with hemophilia A. Hemophilia A is a congenital FVIII deficiency. In this disorder the patient makes less FVIII and therefore needs replacement therapy with FVIII to either stop or prevent bleeding episodes. rVIII-SingleChain can be used for all age groups (see Package Leaflet for the full indication). The active ingredient in rVIII-SingleChain is Lonoctocog alfa. rVIII-SingleChain is administered via an intravenous injection into the patient's vein. The medicine is provided as a powder supplied in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 2500, and 3000 IU doses. Each pack contains a vial with Water for Injection (2.5 or 5 mL) for reconstitution of the powder.

Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Recombinant Single-Chain Factor VIII (rVIII-SingleChain), together with measures to minimize such risks and the proposed studies for learning more about rVIII-SingleChain'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 ("Arzneimittelinformation/ Information sur le médicament") 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 to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (eg, 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 analyzed, including Periodic Safety Update Report 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 rVIII-SingleChain is not yet available, it is listed under 'missing information' below.

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List of important risks and missing information

Important risks of rVIII-SingleChain 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 rVIII-SingleChain. Potential risks are concerns for which an association with the use of this medicine is possible based on available data (class effect), but the association with rVIII-SingleChain 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	• Hypersensitivity and anaphylactic reactions • Development of inhibitors
Important potential risks	• Dosing errors based on assay type (ChS vs OS) used for monitoring of FVIII levels
Missing information	• Experience in pregnancy and lactation, including labor and delivery • Experience in geriatric patients (65 years and above) • Experience of use in patients for ITI (off-label use)

ChS = chromogenic substrate; FVIII = coagulation factor VIII; ITI = immune tolerance induction; OS = one-stage.

Summary of important risks

Important identified risk: Hypersensitivity and Anaphylactic Reactions	
Evidence for linking the risk to the medicine	Published literature, clinical studies, and post-marketing data. Across the SmPCs of the product class of FVIII therapies, Hypersensitivity is a frequently documented ADR. With use of some FVIII products, cases of hypersensitivity have progressed and were associated with anaphylaxis.
Risk factors and risk groups	People with known hypersensitivity to rVIII-SingleChain or its excipients, including hamster protein are at risk. General factors that increase the likelihood of Type 1 hypersensitivity include repeated exposure to the medicinal product and a history of hypersensitivity to a medicinal product of the same class.
Risk minimization measures	Routine risk minimization measures SmPC section 4.3 and 4.8 SmPC section 4.4 where advice is given on signs of hypersensitivity, discontinuation of treatment, and contacting the physician, and information is given to consider appropriate premedication Prescription only medicine Additional risk minimization measures None.
Additional pharmacovigilance activities	Study 3001 (phase III extension study) EUHASS PedNet

	See below for an overview of the post-authorization development plan.

Important identified risk: Development of Inhibitors	
Evidence for linking the risk to the medicine	Published literature, clinical studies, and post marketing data. The main risk associated with FVIII replacement therapy, whether based on plasma derived or recombinant products, is the development of inhibitors (ie, neutralizing antibodies) against FVIII, rendering treatment with antihemophilic factors less effective or ineffective. This risk is recognized as being significantly higher in PUPs, in whom treatment with any antihemophilic factor presents a risk of inhibitor formation as the risk has been estimated to be up to 35.4%. The development of an inhibitor can be associated with significant morbidity and mortality, including a higher rate of bleeding complications, increased disability, and a decreased quality of life. Of note, the clinical relevance of inhibitor development overall depends on the titer of the inhibitor, with low titer inhibitors (0.6 to < 5 BU/mL) which are transiently present or remain consistently low titer posing less of a risk of insufficient clinical response than high titer inhibitors (≥ 5 BU/mL).
Risk factors and risk groups	Risk factors for developing inhibitors include: • Host related mutation: null mutations, larger deletions, intron 1 and 22 inversion, and small missense mutations • Ethnicity: 2 to 5-fold increase associated with patients of Hispanic and African origin compared to Caucasians • Family history: increased risk with first degree family history of inhibitors • Age: inhibitors are likely to develop in subjects < 5 years and > 60 years • Treatment-related EDs: risk highest during early exposure, with a median time of inhibitor presentation at approximately 10 to 15 EDs, and risk subsequently falling after 50 EDs • Severity of hemophilia A • Early FVIII treatment exposure • Switching FVIII products • Previous history of inhibitors • Recent pro-inflammatory conditions such as bleeds, infections, vaccinations, etc., called danger signals. The REMAIN (REal life MAnagement of INhibitors) study (follow-up study of the PedNet Registry and the CANAL study) which included 260 children with severe hemophilia A and newly diagnosed inhibitors born between 1990 and 2009 from 31 hemophilia treatment centers revealed that the presence of null F8 mutations and a positive family history were risk factors for progression from low to high titer inhibitors in a univariate logistic regression analysis. Use of high-dose immune tolerance induction (defined as ≥ 100 IU FVIII concentrate/kg/d) was found to be a risk factor for progression to high titer inhibitors in a cox regressional analysis. With respect to product type, a similar proportion of patients treated with either product type progressed to high-titer inhibitors. For anti-CHO cell antibodies, patients with known allergy to hamster protein are at risk.

Risk minimization measures	Routine risk minimization measures SmPC section 4.8 SmPC section 4.4 where advice is given on monitoring for development of neutralizing antibodies and management of patients with high levels of inhibitor to be directed by physicians with experience in the care of hemophilia and FVIII inhibitors, and information is given about risk factors and clinical relevance of inhibitors depending of titers Prescription only medicine Additional risk minimization measures None.
Additional pharmacovigilance activities	Study 3001 (phase III extension study) EUHASS ATHN 8 PedNet See below for an overview of the post-authorization development plan.

Important potential risk – Dosing Errors Based on Assay Type (ChS vs OS) Used for Monitoring of FVIII Levels	
Evidence for linking the risk to the medicine	Published literature, clinical studies, and post marketing data. No symptoms of overdose with rVIII-SingleChain have been reported. One patient was reported to have received more than double the prescribed dose, with no related adverse events were reported with this overdose. There have also been no cases reported of events associated with Dosing Errors Based on Assay Type (ChS vs OS) Used for Monitoring of FVIII Levels. Even if an OS assay result were interpreted without adjustment with the correction factor, and in an unlikely scenario that resultant FVIII level reached up to 200%, the FVIII activity would still be below the acute phase reactant levels of up to 240% that have been documented in individuals without congenital bleeding disorders. These acutely high physiological levels have not been linked with any adverse reactions in scientific literature.
Risk factors and risk groups	Patients whose healthcare practitioners and / or local laboratories interpret results from the OS clotting assay without taking into account adequate guidance as provided in the rVIII-SingleChain SmPC are at risk.
Risk minimization measures	Routine risk minimization measures SmPC section 4.2 and 4.4 where advice is given on treatment monitoring and multiplication of result by a conversion factor of 2.0 if the OS clotting assay is used, and information is given about discrepancies of OS clotting assay results versus chromogenic assay results Prescription only medicine Additional risk minimization measures None.
Additional pharmacovigilance activities	Study 3001 (phase III extension study) See below for an overview of the post-authorization development plan.

Missing information: Experience in pregnancy and lactation, including labor and delivery

Risk minimization measures	Routine risk minimization measures SmPC section 4.6 Prescription only medicine Additional risk minimization measures None.

Missing information: Experience in geriatric patients (65 years and above)	
Risk minimization measures	Routine risk minimization measures SmPC section 4.2 Prescription only medicine Additional risk minimization measures None.

Missing information: Experience of use in patients for ITI (off-label use)	
Risk minimization measures	Routine risk minimization measures Prescription only medicine Additional risk minimization measures None.
Additional pharmacovigilance activities	Study 3001 (phase III extension study). See below for an overview of the post-authorization development plan.

ADR = adverse drug reaction; ATHN = American Thrombosis and Hemostasis Network; BU = Bethesda unit; CHO = chinese hamster ovary; ChS = chromogenic substrate; ED = exposure day; EUHASS = European Haemophilia Safety Surveillance; FVIII = coagulation factor VIII; ITI = immune tolerance induction; NIS = non interventional study; OS = one-stage; PedNet = Pediatric Network (Haemophilia Registry); PUP = previously untreated patients; rVIII-SingleChain = Recombinant SingleChain factor VIII; SmPC = summary of product characteristics.

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Post-authorization development plan

Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of rVIII-SingleChain.

Other studies in post-authorization development plan

Study 3001: A Phase III Open Label, Multicenter, Extension Study to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (rVIII-SingleChain, CSL627) in Subjects with Severe Hemophilia A

Purpose of the study: CSL Behring is conducting a post marketing safety study (Study 3001) that will provide data to comply with the post marketing requirements of FVIII products, as documented in the EU clinical trial guideline (EMA, 2012; EMA 2018). This study will provide additional data on efficacy and safety including immunogenicity and inhibitor development.

EUHASS

Purpose of the study: CSL Behring participates in this ongoing pharmacovigilance program monitoring the safety of treatments for people with inherited bleeding disorders in Europe to obtain long-term post-marketing safety data (including hypersensitivity and inhibitor development).

ATHN 8

Purpose of the study: To inform treatment strategies for young children with hemophilia, and to document current treatment patterns in young children with hemophilia, document rates of inhibitor formation across factor replacement products, and evaluate determinants of inhibitor formation.

PedNet

Purpose of the study: To collect all data on treatment, side effects and outcome of treatment on all hemophilia patients including but not limited to PUPs.

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Summary of changes to the Swiss RMP Summary over time

Version	Date	Change	Comment
01	23-Jan-2017	Initial document	Initial document, based on EU RMP Version 3.1, 05-Dec-2016
02	29-Jan-2019	1. The risk 'Development of antibodies against CHO host cell proteins' previously classified as important potential risk has been embedded within the text of the important identified risks of 'Hypersensitivity/Anaphylactic reactions' and 'Development of inhibitors'. 2. The missing information 'Experience of inhibitor formation in PUPs' was removed.	Version based on EU Risk Management Plan Version 4.0; 24-Nov-2018 Required changes due to usage of new EU-RMP template as per GVP Module V Rev. 2; comprehensive revision/update of entire summary of RMP document.
03	03-Mar-2020	Updated information on registries/non-interventional study to reflect only those which are considered additional pharmacovigilance activities, category 3 (addition of registry ATHN 8, removal of registries ATHN 2 and Dutch Hemophilia Registry as well as the AFSTYLA NIS); also to demonstrate how PUP data will be complemented. Data have been updated to the DLP of 03 July 2019 to be consistent with EU PSUR No. 5	Version based on EU Risk Management Plan Version 5.0; 27-Nov-2019