CSL Behring

Afstyla

INN: Lonoctocog alfa

Swiss Summary to the Risk Management Plan

Version number of RMP: 6.1

Marketing Autorisation Holder: CSL Behring Lengnau AG

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of 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 Lengnau AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Afstyla.

The medicine and what it is used for

rVIII-SingleChain is a human clotting (coagulation) factor VIII product that is produced by recombinant DNA technology. rVIII-SingleChain is authorized for the treatment and prevention of bleeding episodes in patients with haemophilia A (inborn factor VIII deficiency). Factor VIII is a protein needed for blood to clot. Patients with haemophilia A lack this factor, so blood does not clot as quickly as it should, and they have an increased tendency to bleed. rVIII-SingleChain works by replacing the missing factor VIII in haemophilia A patients enabling their blood to clot normally. rVIII-SingleChain can be used for all age groups (see Package Leaflet for the full indication). rVIII-SingleChain contains Lonoctocog alfa as the active substance and is administered via an intravenous injection into the patient's vein.

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

- https://www.ema.europa.eu/en/medicines/human/EPAR/afstyla#assessment-history-section
- https://www.ema.europa.eu/documents/assessment-report/afstyla-epar-public-assessment-report_en.pdf

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 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.

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, 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 (eg, 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	None
Missing information	None

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.

Important identified risk: Hypersensitivity and Anaphylactic Reactions	
	Additional risk minimization measures None.
Additional pharmacovigilance activities	EUHASS PedNet See section II.C of this summary 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%, or up to a product-dependent global cumulative incidence of 50.1%. 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). The safety and efficacy of rVIII-SingleChain in PUPs with severe hemophilia A was investigated in the completed arm 2 of the multicenter, nonrandomized, open-label, phase 3 extension study (CSL627_3001). A total of 24 subjects were included in the study, receiving at least 1 dose of rVIII-SingleChain during the study either as on-demand or prophylaxis regimen. Of the 24 subjects, 12 subjects (50%) tested positive for inhibitor development. Overall, 6 subjects (25%) had a peak inhibitor value in the high-titer range, and 6 subjects (25%) in the low-titer range. The initial inhibitor result was observed at a median ED 9 and 10, for subjects in the high titer and low titer range, respectively. Eleven subjects were treated for their inhibitor, and 9 subjects (81.8%, 6 low-titer and 3 high titer inhibitors) achieved inhibitor eradication with rVIII-SingleChain. No new safety concerns were observed in this study. The safety profile of rVIII-SingleChain in PUPs is largely consistent with that observed in PTPs.

Important identified risk: Development of Inhibitors	
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.
Risk Minimization measures	Routine risk minimization measures SmPC section 4.8 SmPC section 4.4: advice on monitoring for development of neutralizing antibodies and management and on management of patients with high levels of inhibitor to be directed by physicians with experience in the care of hemophilia and FVIII inhibitors. Information on risk factors and clinical relevance of inhibitors depending of titers. Prescription only medicine. Additional risk minimization measures None.
Additional pharmacovigilance activities	EUHASS ATHN 8 PedNet See section II.C of this summary for an overview of the post-authorization development plan.

ATHN = American Thrombosis and Hemostasis Network; BU = Bethesda unit; ED = exposure day; EUHASS = European Haemophilia Safety Surveillance; FVIII = coagulation factor VIII; PedNet = Pediatric Network (Haemophilia Registry); PTP = previously treated patient; PUP = previously untreated patient; 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

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 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

Version	Date	Change History	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
04	15-Feb-2024	Dosing Errors Based on Assay Type (ChS vs OS) Used for Monitoring of FVIII Levels, Experience in pregnancy and lactation, Experience in geriatric patients (65 years and above), and Experience of use in patients for ITI (off-label use) are removed from the list of safety concerns. Study CSL627_3001 (PUP arm) was completed and updated information is provided.	Version based on EU Risk Management Plan Version 6.1; 03-May-2022