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Idelvion

Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) / albutrepenonacog alfa

Swiss Summary of Risk Management Plan

Version number of RMP: 3.1

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 Idelvion 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 Idelvion 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 Idelvion.

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The medicine and what it is used for

Idelvion is authorized for treatment and prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency). It contains Albutrepenonacog alfa as the active substance and it is given by injection for intravenous use.

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

Important risks of Idelvion, together with measures to minimize such risks and the proposed studies for learning more about Idelvion'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 (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 Idelvion is not yet available, it is listed under 'missing information' below.

List of important risks and missing information

Important risks of Idelvion 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 Idelvion. 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	• Hypersensitivity / anaphylactic reactions • Development of inhibitors to factor IX
Important potential risks	• TEEs • Development of antibodies against CHO host cell proteins • Dosing errors based on variability in the assays used during treatment monitoring of factor IX levels
Missing information	• Experience in patients with severe renal or hepatic impairment • Efficacy and safety in PUPs • Experience in pregnancy and lactation, including labor and delivery • Experience in elderly patients (aged 65 years and above) • Experience in patients for ITI (off-label use)

CHO, Chinese hamster ovary; ITI, immune tolerance induction; PUPs, previously untreated patients; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; TEEs, thromboembolic events

Summary of important risks

Important identified risk - Hypersensitivity/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 FIX therapies, Hypersensitivity is rarely documented. With use of some FIX products, cases of hypersensitivity have progressed and were associated with anaphylaxis.
Risk factors and risk groups	People with known hypersensitivity to Idelvion or its excipients, including people with allergies to hamster proteins. 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 section 4.8 SmPC section 4.4 where advice is given on symptoms of hypersensitivity, discontinuation of treatment, and contacting the physician. Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003 Participation in EUHASS

EUHASS = European Haemophilia Safety Surveillance

Important identified risk - Development of inhibitors to factor IX	
Evidence for linking the risk to the medicine	Published literature, clinical studies, and post-marketing data. The main risk associated with FIX replacement therapy, whether based on plasma derived or recombinant products, is the development of inhibitors (ie, neutralizing antibodies) against FIX, rendering treatment with antihemophilic factors less effective or ineffective. It is noted that the incidence of inhibitors in patients following administration of factor IX is less common compared to the incidence found in hemophilia A patients. Inhibitors to factor IX have been demonstrated in approximately 1.5 to 5% of patients with severe hemophilia B.
Risk factors and risk groups	The risk factors for factor IX inhibitor formation have not been extensively studied, in part due to the relative rarity of the event. Inhibitor development is generally associated with the absence of factor IX due to major deletions or nonsense mutations of the factor IX gene. Individuals with small deletions or missense mutations have a lower risk of inhibitor formation.
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, mention of additional risk factors and initial administration of Idelvion should be done by trained physician and under medical observation. Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003 Participation in EUHASS

EUHASS = European Haemophilia Safety Surveillance

Important potential risk – thromboembolic events (TEEs)	
Evidence for linking the risk to the medicine	Published literature, clinical studies, and post marketing data.
Risk factors and risk groups	Given improved long term survival rates, patient risks are similar as in the general population and include: *Thrombosis risks:* • Pregnancy • Hormone replacement therapy • Surgery • Immobilization • Trauma • Cancer • Smoking • Hypertension • Hypercholesterolemia • Peripheral vascular disease • Diabetes • Obesity

Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 SmPC section 4.4 Advice is given to mitigate the risk through clinical surveillance and clinical monitoring with appropriate biological testing when administering Idelvion to special populations (patients with liver disease, to patients post-operatively, to newborn infants, or to patients at risk of thrombotic phenomena or disseminated intravascular coagulation). Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003 Participation in EUHASS

EUHASS = European Haemophilia Safety Surveillance; TEEs = thromboembolic events

Important potential risk - Development of antibodies against CHO host cell proteins	
Evidence for linking the risk to the medicine	Published literature.
Risk factors and risk groups	Known allergy to hamster protein (contraindication for Idelvion).
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3 and section 4.8 SmPC section 4.4 where advice is given on the signs of hypersensitivity, discontinuation of the treatment, and contacting the physician Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003 Participation in EUHASS

CHO = Chinese hamster ovary

Important potential risk - Dosing errors based on variability in the assays used during treatment monitoring of factor IX levels	
Evidence for linking the risk to the medicine	EMA workshop report: Characterization of new clotting factor concentrates (FVIII, factor IX) with respect to potency assays used for labeling and testing of post injection samples. EMA/135928/2014. November 2013.
Risk factors and risk groups	All patients receiving recombinant factor IX products are potentially at risk of dosing errors based on the variability in the assays used during treatment monitoring of factor IX levels.

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Risk minimization measures	Routine risk minimization measures: SmPC section 4.2 gives advice on treatment monitoring using one stage clotting assay and other factors which may significantly underestimate activity levels Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003

Missing information - Experience in patients with severe renal or hepatic impairment	
Risk minimization measures	Routine risk minimization measures: Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003 Participation in EUHASS

Missing information - Efficacy and safety in PUPs	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2 states the safety and efficacy of Idelvion in previously untreated patients have not yet been established. In SmPC section 4.4 Pediatric patients, it indicates the listed warnings and precautions apply both to adults and children. Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003 Participation in EUHASS

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
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pregnancy and Outcome Questionnaires

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Missing information - Experience in elderly patients (aged 65 years and above)	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Participation in EUHASS

Missing information - Experience with patients in ITI (off-label use)	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 states the safety and efficacy of using Idelvion for immune tolerance induction has not been established. SmPC section 4.8 states that nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction. Prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Participation in EUHASS

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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 obligations for Idelvion.

Other studies in post-authorization development plan

CSL654_3003/ Clinical study: A Phase 3b open label, multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B, including PUPs

Purpose of the study: CSL654_3003 is intended as the post-marketing investigation as stipulated in Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009).
The objective of the main study is to evaluate the safety of rIX-FP as measured by new cases of inhibitors against factor IX.
The objective of the surgery substudy is to evaluate the efficacy of rIX-FP in the prevention and control of bleeding in subjects with severe hemophilia B during surgical procedures.

European Haemophilia Safety Surveillance (EUHASS)

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).

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Summary of changes to the Swiss RMP Summary over time

Version	Date	Safety concerns	Comment
01	13-Oct-2016	Initial document	Initial document, based on EU RMP Version 1.0, 20-Feb-2015
02	03-Jan-2017	**Summary of Safety concerns:** Risks re-classified • Allergic reactions and formation of neutralizing antibodies changed from potential to identified risks • Thromboembolic events changed from missing information to potential risks • Patients with severe renal of hepatic impairment added to missing information • Unauthorized use of rIX-FP in ITP added to missing information	Upon EMA's request and to follow the guideline on clinical investigation of recombinant and human plasma derived factor IX products (EMA/CHMP/BPWP/144552/2009)
03	09-Jun-2020	• "Anaphylactic reactions" with "hypersensitivity" included as important identified risk. • "Ongoing study 3003" and "participation with EUHASS" added as required additional pharmacovigilance activities. • All RMP modules have been revised in accordance with requirements of GVP V Revision 2. Data has been updated to the DLP of 26-Jan-2019, to be consistent with PSUR 5. • Updated information regarding the completion of study CSL654_3003 (excluding PUP arm, which remains ongoing)	Version based on EU Risk Management Plan Version 3.1; 15-Jul-2019