

## **Summary of the risk management plan**

### **Summary of risk management plan for Idelvion (Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin(rIX-FP))**

This is a summary of the risk management plan (RMP) for Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) Idelvion . The RMP details important risks of Idelvion, how these risks can be minimized, and how more information will be obtained about Idelvion's risks and uncertainties (missing information).

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

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

#### **I. 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). (see SmPC for the full indication). It contains Albutrepenonacog alfa as the active substance and it is given by injection for intravenous use.

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

<https://www.ema.europa.eu/en/medicines/human/EPAR/idelvion>

#### **II. 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 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 analyzed, including in PSUR assessments, 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.

## **II.A 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);

<b>List of important risks and missing information</b>	
Important identified risks	<ul style="list-style-type: none"> <li>• Hypersensitivity / anaphylactic reactions</li> <li>• Development of inhibitors to factor IX</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• TEEs</li> <li>• Development of antibodies against CHO host cell proteins</li> <li>• Dosing errors based on variability in the assays used during treatment monitoring of factor IX levels</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Experience in patients with severe renal or hepatic impairment</li> <li>• Efficacy and safety in PUPs</li> <li>• Experience in pregnancy and lactation, including labor and delivery</li> <li>• Experience in elderly patients (aged 65 years and above)</li> <li>• Experience in patients for ITI (off-label use)</li> </ul>
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	

## II.B Summary of important risks

<b>Important identified risk - Hypersensitivity/anaphylactic reactions</b>	
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	<u>Routine risk minimization measures:</u> 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 <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical study CSL654_3003 Participation in EUHASS

<b>Important identified risk - Development of inhibitors to factor IX</b>	
Evidence for linking the risk to the medicine	<p>Published literature, clinical studies, and post-marketing data.</p> <p>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.</p>
Risk factors and risk groups	<p>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.</p>
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>SmPC section 4.8</p> <p>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.</p> <p>Prescription only medicine</p> <p><u>Additional risk minimization measures:</u></p> <p>None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p>Clinical study CSL654_3003</p> <p>Participation in EUHASS</p>

<b>Important potential risk – thromboembolic events (TEEs)</b>	
Evidence for linking the risk to the medicine	Published literature, clinical studies, and post marketing data.
Risk factors and risk groups	<p>Given improved long term survival rates, patient risks are similar as in the general population and include:</p> <p><i>Thrombosis risks:</i></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Hormone replacement therapy</li> <li>• Surgery</li> <li>• Immobilization</li> <li>• Trauma</li> <li>• Cancer</li> <li>• Smoking</li> <li>• Hypertension</li> </ul>

<b>Important potential risk – thromboembolic events (TEEs)</b>	
	<ul style="list-style-type: none"> <li>• Hypercholesterolemia</li> <li>• Peripheral vascular disease</li> <li>• Diabetes</li> <li>• Obesity</li> </ul>
Risk minimization measures	<p><u>Routine risk minimization measures:</u> SmPC section 4.8 SmPC section 4.4</p> <p>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).</p> <p>Prescription only medicine</p> <p><u>Additional risk minimization measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u> Clinical study CSL654_3003 Participation in EUHASS</p>

<b>Important potential risk - Development of antibodies against CHO host cell proteins</b>	
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	<p><u>Routine risk minimization measures:</u> SmPC section 4.3 and section 4.8</p> <p>SmPC section 4.4 where advice is given on the signs of hypersensitivity, discontinuation of the treatment, and contacting the physician</p> <p>Prescription only medicine</p> <p><u>Additional risk minimization measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u> Clinical study CSL654_3003 Participation in EUHASS</p>

<b>Important potential risk - Dosing errors based on variability in the assays used during treatment monitoring of factor IX levels</b>	
Evidence for linking the risk to the medicine	<a href="#">EMA workshop report</a> : Characterization of new clotting factor concentrates (FVIII, factor IX) with respect to potency assays used for labeling and testing of post injection samples. 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.
Risk minimization measures	<u>Routine risk minimization measures:</u> 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 <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Clinical study CSL654_3003

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

<b>Missing information - Efficacy and safety in PUPs</b>	
Risk minimization measures	<u>Routine risk minimization measures:</u> 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 <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Clinical study CSL654_3003 Participation in EUHASS
<b>Missing information - Experience in pregnancy and lactation, including labor and delivery</b>	

Risk minimization measures	<u>Routine risk minimization measures:</u> SmPC section 4.6 Prescription only medicine <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Pregnancy and Outcome Questionnaires

**Missing information - Experience in elderly patients (aged 65 years and above)**

Risk minimization measures	<u>Routine risk minimization measures:</u> SmPC section 4.4 Prescription only medicine <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Participation in EUHASS

**Missing information - Experience with patients in ITI (off-label use)**

Risk minimization measures	<u>Routine risk minimization measures:</u> 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 <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Participation in EUHASS

## **II.C Post-authorization development plan**

### **II.C.1 Studies which are conditions of the marketing authorization**

There are no studies which are conditions of the marketing authorization or specific obligations for Idelvion.

### **II.C.2 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)**

##### 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).