Part VI: Summary of the risk management plan

Summary of risk management plan for Hizentra (Human normal immunoglobulin for subcutaneous use (SCIg))

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

Hizentra's reference safety information (referred to as the Summary of Product Characteristics [SmPC] and the Patient Information Leaflet [PIL] in Europe), give essential information to healthcare professionals and patients on how Hizentra should be used.

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

I. The medicine and what it is used for

Hizentra is authorised for replacement therapy in Primary Immunodeficiency Disease (PID) and symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment; as well as an immunomodulatory therapy in chronic inflammatory demyelinating polyneuropathy (CIDP). Refer to the product's reference safety information (the SmPC and PIL in Europe) for full information on indications. It contains human normal immunoglobulin as the active substance, and it is given by subcutaneous infusion.

Further information about the evaluation of Hizentra's benefits can be found in Hizentra's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link: https://www.ema.europa.eu/en/medicines/human/EPAR/hizentra.

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

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

- Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, which are addressed in the reference safety information (the SmPC and PIL in Europe) for healthcare professionals and patients;
- Important advice on the medicine's packaging;
- The authorised 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 (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Hizentra are risks that need special risk management activities to further investigate or minimise 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 Hizentra. 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 (eg, on the long-term use of the medicine):

List of important risks and missing information	
Important identified risks	• Local Reactions including ulceration like-infusion site reactions (UL-ISRs) • Anaphylactic reactions • Aseptic Meningitis Syndrome (AMS) • Thromboembolic events (TEE)
Important potential risks	• Increased or unknown risks in the home-based SC (self-) administration • Exacerbation of existing hyperprolinaemia • Haemolysis • Transmission of infectious agents
Missing information	• None

AMS = aseptic meningitis syndrome; SC = subcutaneous; TEE = thromboembolic events; UL-ISR = ulceration like-infusion site reactions.

II.B Summary of important risks

Important identified risk: Local reactions including UL-ISRs	
Evidence for linking the risk to the medicine	There is significant evidence from numerous case reports of local reactions observed from post-marketing surveillance and clinical trials (frequency: very common). Additionally, evidence from the scientific literature supports a causal association with SCIg products. This risk is a known class effect of SCIg products, and is considered an adverse reaction occurring with high frequency in the indicated populations, which could have a severe impact (eg, discontinuation of treatment).
Risk factors and risk groups	Most patients experience mild local reactions, even on stable dosing, suggesting that other individual factors may be the key drivers of local reactions, in contrast to dosing. Specific risk groups or risk factors are not known, and relevant information from CSLB's large outcome studies did not identify any clear risk groups/factors, nor any association between higher doses, infusion rates or volume and a higher rate of local reactions. Similarly, no specific risk groups or risk factors for the development of UL-ISRs (including infusion site necrosis) have been identified since the etiology for the occurrence is not clearly understood.
Risk minimisation measures	Routine risk minimisation measures Undesirable effects section of RSI Additional risk minimisation measures None

CSLB = CSL Behring; RSI = reference safety information; SCIg = subcutaneous immunoglobulin; UL-ISR = ulceration like-infusion site reactions.

Important identified risk: Anaphylactic reactions	
Evidence for linking the risk to the medicine	A limited number of anaphylactic reaction case reports have been observed from post-marketing surveillance, however there have been no cases from clinical trials (frequency: unknown). Additionally, evidence from the scientific literature supports a causal relationship with Ig products, including SCIg. This risk is a known class effect of Ig products, and is considered serious due to the potential life-threatening nature.
Risk factors and risk groups	General risk factors for drug allergy include age (more likely in adults), gender (female), genetic polymorphisms, certain viral infections, and previous reaction to the drug. Additionally, parenteral route and/or frequent/prolonged administration are considered more immunogenic. Specifically, Hizentra may present an increased risk of anaphylaxis in IgA deficient patients as it contains traces of IgA, however the role of IgA in anaphylactic reactions is often described as controversial. Many

Important identified risk: Anaphylactic reactions	
	patients with low IgA levels tolerate products that are not specifically designated as low IgA.
Risk minimisation measures	Routine risk minimisation measures Undesirable effects, Contraindications, and Warnings & precautions for use sections of RSI Additional risk minimisation measures None

Ig = immunoglobulin; IgA = immunoglobulin A; RSI = reference safety information; SCIg = subcutaneous immunoglobulin.

Important identified risk: Aseptic Meningitis Syndrome (AMS)	
Evidence for linking the risk to the medicine	A limited number of AMS case reports have been observed from post-marketing surveillance and clinical trials (frequency: uncommon). Additionally, evidence from the scientific literature supports a causal relationship with Ig products, predominantly IVIg. This risk is a known class effect of Ig products, which could have a severe impact (eg, medical intervention, discontinuation of treatment).
Risk factors and risk groups	In patients treated with IVIg, high dosages infused over short periods may be a risk factor, however the development of AMS is not limited to high dosages, and has been observed with typical replacement dosages. Other risk factors for AMS include: - a history of headache or migraine; however it remains questionable if such pre-existing disorders play a major role; - hypertensive disease; - dehydration; - female patients, with an approximate 4-fold higher rate; - children with autoimmune diseases. Data indicates that aseptic meningitis occurs significantly less often after SCIg therapy than IVIg therapy.
Risk minimisation measures	Routine risk minimisation measures Undesirable effects and Warnings & precautions for use sections of RSI Additional risk minimisation measures None

AMS = aseptic meningitis syndrome; Ig = immunoglobulin; IVIg = intravenous immunoglobulin; RSI = reference safety information; SCIg = subcutaneous immunoglobulin.

Important identified risk: Thromboembolic Event (TEE)	
Evidence for linking the risk to the medicine	A limited number of TEE case reports have been observed from post-marketing surveillance, however there have been no serious, related cases from clinical trials (frequency: unknown). Additionally, evidence from the scientific literature supports a causal relationship with Ig products, predominantly IVIg. This risk is a known class effect of Ig products, and is considered serious due to the potential life-threatening nature of certain types of TEE.
Risk factors and risk groups	• Advanced age • Hypertension, cardiovascular risk factors • Diabetes mellitus • History of vascular disease or thrombotic episodes • Acquired or inherited thrombophilic disorders • Hypercoagulable conditions • Use of estrogens • Indwelling vascular catheters • Prolonged periods of immobilisation • Severely hypovolemic patients • Any disease or condition which increases blood viscosity
Risk minimisation measures	Routine risk minimisation measures Undesirable effects and Warnings & precautions for use sections of RSI Additional risk minimisation measures None

Ig = immunoglobulin; IVIg = intravenous immunoglobulin; RSI = reference safety information; TEE = thromboembolic event.

Important potential risk: Increased or unknown risks in the home-based SC (self-) administration	
Evidence for linking the risk to the medicine	On the basis of theoretical considerations, increased or unknown risks in the home-based SC (self-) administration is considered to have the potential for a severe impact (eg, medical intervention, discontinuation of treatment). A limited number of reports have been observed from post-marketing surveillance, however there is no information from clinical trials (frequency: unknown).
Risk factors and risk groups	Patients using home-based SC (self-) administration.
Risk minimisation measures	Routine risk minimisation measures Information on method and route of administration: Posology & method of administration and Warnings & precautions for use sections of RSI Additional risk minimisation measures None

RSI = reference safety information; SC = subcutaneous.

Important potential risk: Exacerbation of existing hyperprolinaemia	
Evidence for linking the risk to the medicine	On the basis of theoretical considerations, exacerbation of existing hyperprolinaemia is considered to have the potential for a severe impact (eg, medical intervention, discontinuation of treatment). There is no information from post-marketing surveillance or clinical trials (frequency: unknown).
Risk factors and risk groups	Individuals with the genetic disorder of hyperprolinaemia Type I or II.
Risk minimisation measures	Routine risk minimisation measures Contraindications section of RSI Additional risk minimisation measures None

RSI = reference safety information.

Important potential risk: Haemolysis	
Evidence for linking the risk to the medicine	A limited number of haemolysis case reports have been observed from post-marketing surveillance, however there have been no related cases from clinical trials (frequency: unknown). Additionally, evidence from the scientific literature supports a causal relationship with Ig products, predominantly IVIg. This risk is a known class effect of Ig products, which could have a severe impact (eg, medical intervention, discontinuation of treatment).
Risk factors and risk groups	Risk factors for hemolysis include high-dose infusions, underlying recipient health conditions (eg, inflammatory conditions, autoimmune, or immune-mediated disorders), prior episode of haemolysis, and non-O blood group. Differences in immunoglobulin products manufacturing processes resulting in higher titers of anti-A and anti-B isoagglutinins may also play a role, with 1 study showing that products with high anti-A/anti-B titers have elevated haemolysis reaction reporting rates, particularly when larger cumulative doses were administered.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None

Ig = immunoglobulin; IVIg = intravenous immunoglobulin.

Important potential risk: Transmission of infectious agents	
Evidence for linking the risk to the medicine	There have been no confirmed cases from post-marketing surveillance or clinical trials, however the risk of transmission of infectious agents cannot be totally excluded when medicinal products prepared from human blood/plasma are administered. Historically, viral transmission cases (eg, HBV, HCV) have been reported in the scientific literature for other older Ig products (lyophilised preparations only), which occurred prior to the recognition of the importance of donor selection criteria, serological screening, and effective and well-validated viral removal and inactivation processes. This risk is considered serious due to the life-threatening nature and potential for death.
Risk factors and risk groups	Patients administered medicinal products prepared from human blood/plasma.
Risk minimisation measures	Routine risk minimisation measures Warnings & precautions for use section of RSI Additional risk minimisation measures None

HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; RSI = reference safety information.

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 Hizentra.

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

There are no studies required for Hizentra.