Berinert®

(C1 Esterase Inhibitor, Human (C1-INH))

Public Summary of Risk Management Plan

(Extract from the EU Risk Management Plan Version 5.1; 24-Dec-2019)

Part VI: Summary of the risk management plan

Summary of risk management plan for C1 Esterase Inhibitor, Human (C1-INH) Berinert IV and Berinert SC

This is a summary of the risk management plan (RMP) for Berinert IV and Berinert SC. The RMP details important risks of Berinert IV and Berinert SC, how these risks can be minimized, and how more information will be obtained about Berinert IV and Berinert SC's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

Berinert IV is authorized for hereditary angioedema type 1 and 2, treatment and pre-procedure prevention of acute episodes and Berinert SC is authorized for prevention of recurrent hereditary angioedema attacks in adolescent and adult patients with C1 –esterase inhibitor deficiency. It contains C1 esterase inhibitor, human as the active substance; Berinert IV is given by intravenous administration and Berinert SC is given by subcutaneous administration.

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

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

II.A List of important risks and missing information

Important risks of Berinert IV and Berinert SC 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 Berinert IV and Berinert SC. 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	
Berinert IV	
Important identified risks	• Hypersensitivity/anaphylactic reactions • Thromboembolic events • Lack of efficacy
Important potential risks	• Transmission of infectious agents • Off-label use
Missing information	• Limited experience in pregnancy/lactation • Limited experience in pediatric population

	• Limited experience in geriatric population
Berinert SC	
Important identified risks	• Hypersensitivity/anaphylactic reactions
Important potential risks	• Thromboembolic events • Transmission of infectious agents
Missing information	• Limited experience in pregnancy/lactation • Limited experience in pediatric population • Limited experience in geriatric population

II.B Summary of important risks

Important identified risk for Berinert IV and Berinert SC: Hypersensitivity and anaphylactic reactions	
Evidence for linking the risk to the medicine	Data obtained from the CSL Behring safety database with DLP of 23 December 2018.
Risk factors and risk groups	Individuals who have had previous hypersensitivity reactions, including anaphylaxis to C1-INH preparations. The risk is also increased in individuals with prior exposure to other plasma products.
Risk minimization measures	Routine risk minimization measures: *For Berinert IV:* SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 *For Berinert SC:* SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8

	Additional risk minimization measures: None

Important identified risk for Berinert IV and Important potential risk for Berinert SC: TEEs	
Evidence for linking the risk to the medicine	Data obtained from the CSL Behring safety database with DLP of 23 December 2018.
Risk factors and risk groups	Individuals who have known risk factors for thrombotic events including (Previtali et al, 2011): • Older age • Oral contraceptive use • Abnormal lipid profiles • Hypertension • Diabetes • Smoking • Obesity • Trauma and surgery • Medical history of thrombotic events
Risk minimization measures	Routine risk minimization measures: *For Berinert IV:* SmPC Section 4.8 *For CL830:* SmPC Section 4.4 Additional risk minimization measures: None

Important potential risk for Berinert IV: Lack of efficacy	
Evidence for linking the risk to the medicine	Data obtained from CSL Behring safety database with DLP of 23 December 2018.

Risk factors and risk groups	Patients who receive frequent dosing. Berinert IV is not indicated for prophylaxis but repeated dosing might incur a higher risk.
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None

Important potential risk for Berinert IV and Berinert SC: Transmission of infectious agents	
Evidence for linking the risk to the medicine	Data obtained from CSL Behring safety database with DLP of 23 December 2018.
Risk factors and risk groups	Increased with exposure to other blood products. Increased in IV drug users, homosexuals engaged in high-risk sexual behavior, healthcare professionals, and other.
Risk minimization measures	Routine risk minimization measures: *For Berinert IV*: SmPC Section 4.4 *For Berinert SC*: SmPC Section 4.4 Additional risk minimization measures: None

Important potential risk for Berinert IV: Off-label use	
Evidence for linking the risk to the medicine	Data obtained from CSL Behring safety database with DLP of 23 December 2018.
Risk factors and risk groups	Patients at risk of off-label use are those for whom other drugs are

	ineffective (Cinryze), or for whom therapeutic options are limited (eg, HAE type III).
Risk minimization measures	<u>Routine risk minimization measures:</u> *For Berinert IV:* SmPC Section 4.4 SmPC Section 4.8 <u>Additional risk minimization measures:</u> None

Missing information: Limited experience in pregnancy/lactation:	
Risk minimization measures	<u>Routine risk minimization measures:</u> *For Berinert IV:* SmPC Section 4.6 *For Berinert SC:* SmPC Section 4.6 <u>Additional risk minimization measures:</u> None

Missing information: **Limited experience in the pediatric population**	
Risk minimization measures	<u>Routine risk minimization measures:</u> *For Berinert IV:* SmPC Section 5.2 *For Berinert SC:* SmPC Section 5.2 <u>Additional risk minimization measures:</u> None

Missing information: **Limited experience in geriatric population**	
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None

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 obligation of Berinert IV and Berinert SC.

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

CE1145_4001 (Berinert IV only)

Purpose of the study: To assess the formation of inhibitory anti-C1-INH antibodies in subjects with HAE following treatment with Berinert (Study has completed – refer to Annex 2).

CE1145_5002 (Berinert IV only)

Purpose of the study: To create a mechanism for enhanced (active) surveillance of the safety of CSL Behring's C1-INH in "real-world" clinical practice, and to facilitate discovery and reporting of adverse events, including potential thromboembolic events and potential viral transmissions.