VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Hereditary angioedema (HAE) is a disease (present from birth) characterized by blood vessel leakage. It is not an allergic disease. Hereditary angioedema causes attacks caused by deficiency due to the absence or malfunction of an important protein called C1 esterase inhibitor (C1-INH). Hereditary angioedema type 2 occurs when C1-INH does not work properly. The illness is characterized by the following symptoms:

- Swelling of the hands and feet that occurs suddenly,
- Facial swelling with tension sensation that occurs suddenly,
- Eyelid swelling, lip swelling, possibly laryngeal (voice box) swelling with difficulty in breathing, tongue swelling, and
- Colic pain in abdominal region.

Generally, all parts of the body can be affected and sudden attacks of this disease may occur in adolescents and adult patients, especially before medical, dental or surgical procedures.

VI.2.2 Summary of Treatment Benefits

The treatment of choice for an acute attack of HAE is intravenous (iv; through a vein) administration of C1-INH concentrate and the treatment of choice to prevent attacks is subcutaneous (sc; under the skin) administration of CSL830. Berinert and CSL830 are comprised of human plasma C1-INH, which can replace the missing or malfunctioning protein in patients with HAE and can relieve their symptoms.

Berinert

The safety and efficacy of Berinert has been shown in more than 10 studies. Two studies showed that Berinert relieved symptoms of abdominal or facial HAE attacks faster than placebo and within 24 hours in most of the patients. Another study compared the iv and sc administration of Berinert in 24 patients with HAE, where no unexpected risks of sc treatment were observed. The body can produce a type of protein, called an antibody, which can attack drugs, making them ineffective. The formation of antibodies was investigated in a study where 46 patients with HAE were treated with Berinert; no formation of antibodies against Berinert was seen. The transmission of viruses is a risk with Berinert; no proven cases of viral infection were observed in 2 relevant studies with 13 patients with C1-INH deficiency. A Registry collecting information related to 15,000 infusions of Berinert from 318 treated HAE patients over 5 years showed no correlation between Berinert dose and the number of side effects for each treatment. A study where 20 pregnant women were treated with Berinert showed no adverse effects of Berinert in those women, and no harmful effects on the babies. Berinert was also shown to be effective in 30 patients undergoing substitution of C1-INH after extracorporeal circulation (a process where blood is circulated outside of the body, a process is carried out, and the blood returned), where no AEs were reported; the use of Berinert was also effective compared to placebo in those with low C1-INH levels before an operation and for those with heart problems.

CSL830

CSL830 is proposed for the prevention of HAE attacks in adolescent and adult patients and it is intended for sc self-administration. Its efficacy and safety has been shown in 4 studies. In a study of 16 healthy volunteers given CSL830 intravenously, no significant safety concerns were identified. In a study investigating 3 different doses of CSL830 in 18 patients with HAE, no significant safety concerns were identified, and each dose was effective. Another study investigated the effectiveness of CSL830 in the prevention of HAE on 86 HAE patients treated for 16 weeks; treatment with CSL830 reduced the number of HAE attacks. An ongoing study is investigating the long-term prevention of HAE in 120 patients treated with CSL830 for more than 1 year. This study continues to show that CSL830 is effective in preventing HAE attacks. In both studies, no significant safety concerns were identified.

VI.2.3 Unknowns Relating to Treatment Benefits

In the main and supporting studies, nearly all patients were white Caucasians aged between 18 and 65. There is no evidence to suggest that results would be any different in non-white patients or in patients of younger or older ages. Experience in children, the elderly, and pregnant or lactating females is limited, although small numbers in clinical trials and publications suggest that both Berinert and CSL830 are safe and show a similar benefit to populations studied in greater numbers.

VI.2.4 Summary of Safety Concerns

Berinert

Important Identified Risks

Risk	What is known	Preventability
Allergic reactions (hypersensitivity/ anaphylactic reactions)	May occur with use of Berinert, and range from mild (rashes) to severe (shock with fatal outcome).	Berinert should be avoided in cases of allergy to C1-INH or other ingredients of Berinert. Patients should inform their physician about their allergies and take antihistamines or corticosteroids if advised by their physician. In case of serious allergic reaction (with difficulty in breathing or dizziness), Berinert should be stopped immediately. In case of laryngeal swelling, constant monitoring is to be implemented.
Thrombosis or blood clots (thromboembolic events)	These may affect the arteries or veins. In the veins, this may lead to painful swelling of the legs and life-threatening or fatal clots in the lungs. Clots in the arteries may lead to a heart attack or stroke – particularly in patients who already have problems with their arteries.	Patients should inform their physician if they have a history of blood clots, or take blood thinners for any reason. Any other medications taken at the same time with Berinert should be mentioned to the physician.
Lack of efficacy	Over time, antibodies that make Berinert less effective may develop, or higher doses may be needed.	Patients must inform their physician of recurring or worsened symptoms.

C1-INH=C1 esterase inhibitor.

Important potential risks

Potential Risk	What is known (including reason why it is considered a potential risk)
Transmission of infections, such as viruses	When medicines are made from human blood or plasma, measures are taken to prevent infections being passed on to patients. These include: • Careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and • The testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded, which is why transmission of infections is called a “potential risk”. This also applies to any unknown or emerging viruses or other types of infections.
Using the drug for reasons other than HAE (acute treatment or prevention prior to a procedure or surgery)	It is not known if the drug works (is efficacious) or is safe when used for reasons other than those for which the drug is approved (in the indication).

HAE=hereditary angioedema.

Missing information

Risk	What is known
Limited information in pregnancy and breastfeeding	• Pregnant and breastfeeding patients should ask for advice from their physician before taking any medicine. • During pregnancy and breastfeeding, Berinert should be given only if it is clearly needed.
Limited information in children	Available information suggests no differences in children than the adults studied in clinical trials.
Limited information in the older population	Available information suggests no differences in the older population than the adults studied in clinical trials.

CSL830

Important identified risks

Risk	What is known	Preventability
Allergic reactions (hypersensitivity/anaphylactic reactions)	May occur with use of CSL830, and range from mild (rashes) to severe (shock with fatal outcome).	CSL830 should be avoided in cases of allergy to C1-INH or other ingredients of CSL830. Patients should inform their physician about their allergies and take antihistamines or corticosteroids if advised by their physician. In case of serious allergic reaction (with difficulty in breathing or dizziness), CSL830 should be stopped immediately. In case of laryngeal swelling, constant monitoring is to be implemented.

C1-INH=C1 esterase inhibitor.

Important potential risks

Potential Risk	What is known (including reason why it is considered a potential risk)
Thrombosis or blood clots (thromboembolic events)	Thromboembolic events are an important potential risk for CSL830 (as opposed to an important identified risk for Berinert) as there are no case reports with a confirmed causal association between administration of CSL830 and the occurrence of a thromboembolic event. Thromboembolic events may affect the arteries or veins. In the veins, this may lead to painful swelling of the legs and life-threatening or fatal clots in the lungs. Clots in the arteries may lead to a heart attack or stroke – particularly in patients who already have problems with their arteries.
Transmission of infections, such as viruses	When medicines are made from human blood or plasma, measures are taken to prevent infections being passed on to patients. These include: • Careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and

	• The testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded, which is why transmission of infections is called a "potential risk". This also applies to any unknown or emerging viruses or other types of infections.

Missing information

Risk	What is known
Limited information in pregnancy and breastfeeding	Pregnant and breastfeeding patients should ask for advice from their physician before taking any medicine. During pregnancy and breastfeeding, Berinert should be given only if it is clearly needed.
Limited information in children	Available information suggests no differences in children than the adults studied in clinical trials.
Limited information in the older population	Available information suggests no differences in the elderly than the adults studied in clinical trials.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics that provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

The Summary of Product Characteristics and package leaflet for Berinert and CSL830 can be found through the Product Index on the Heads of Medicines Agency website.

These medicines have no additional risk minimization measures.

VI.2.6 Planned Post-authorization Development Plan

Berinert

There is 1 ongoing study in the post-authorization development plan, as presented in Table 40.

Table 40: List of studies (planned or ongoing) in the post-authorization development plan

Study/activity type, title and category (1 to 3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Observational Study of Berinert CE1145_5001 (non-interventional)	To monitor the implementation of the dosage based on body weight under conditions of routine use (real life situation). To collect and evaluate data on the use of the volume-reduced preparation Berinert 1500 IU (as approved by the competent federal authority in December 2014). In addition, data on efficacy and on tolerability will be collected.	Observations regarding safety and tolerability will be analyzed according to clinical description, action taken, frequency, severity, probability of a causal relationship, outcome and correlation with the dose. Adverse drug reactions will be coded using the Medical Dictionary for Regulatory Activities terminology and will be grouped by Preferred Term and System Organ Class.	Started.	31 December 2017

This study is not a condition of the marketing authorization.

CSL830

Not applicable; there are no planned studies/activities in the post-authorization development plan.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

A summary of the changes to the RMP over time is provided in Table 41.

Table 41: Major changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment
Version 1.0	May 2012	**Important identified risks** Hypersensitivity/anaphylactic reactions Thromboembolic events **Important potential risks** Transmission of infectious agents **Missing information** Limited experience in pregnancy/lactation Limited experience in pediatric population Limited experience in geriatric population	No additional risk minimization activities were required.
Version 2.0	June 2013	Lack of efficacy was added as an identified risk, at the request of the	No additional risk minimization activities were required.

Version	Date	Safety concerns	Comment
		Paul-Erlich Institut, as it is a class effect. Off-label use was added as a potential risk, at the request of Health Canada.	
Version 3.0	November 2013	No additional identified or potential risks were added.	No additional risk minimization activities were required.
Version 3.1	March 2015	No additional identified or potential risks were added.	Minor typing errors corrected in Section VI.2.4 (Summary of Safety Concerns).
Version 4.0	December 2016	No additional identified or potential risks were added for Berinert. The RMP was updated to include the proposed sc CSL830 formulation (Berinert 2000 and 3000) with the following safety concerns. **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	
Version 4.1	August 2017	No additional identified or potential risks were added.	Categorization of the studies in the pharmacovigilance plan added for Tables 33 and 34, and EU SmPC attached to Annex 2.
Version 4.2	December 2017	No additional identified or potential risks were added.	Proposed indication for CSL830 updated per RMS Day 180 Response Assessment Report DE/H/0481/003-004/DC

Sc=subcutaneous; RMP=Risk Management Plan.