VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

HAE is a congenital disease of the vascular system. It is a non-allergic disease. HAE is caused by deficiency, absence or defective synthesis of C1-esterase inhibitor, an important protein. 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,
- colic pain in abdominal region.

Generally, all parts of the body can be affected.

VI.2.2 Summary of treatment benefits

The treatment of choice in case of an acute attack of HAE is i.v. administration of C1-INH concentrate or, less preferentially, fresh frozen plasma (FFP). Adrenaline, antihistamines, or androgens can be effective in some subjects as a prophylactic therapy, but may have severe side effects; however, none of these agents is effective in acute attacks.

Corticosteroids, antihistamines or epinephrine usually do not exert any positive effect in acute attacks caused by HAE. This is of particular importance because these types of medication are often used for the treatment of edema in general.

Congenital C1INH deficiency:

Study CE1145_2002 investigated the pharmacokinetics of Berinert in paediatric and adult patients.

Study CE1145_3001 was a prospective, randomized, placebo-controlled, dose-finding, double-blind study. The primary objective was to show that CE1145 shortens the time to onset of relief of symptoms of abdominal or facial HAE attacks compared to Placebo. Secondary objectives were to compare the efficacy of 2 different dosing schemes of CE1145 in abdominal or facial edema attacks due to HAE, and to compare the safety of CE1145 in subjects with HAE between the initial 3 treatment groups (CE1145 10 or 20 U/kg body weight [bw], and Placebo [physiological saline solution. 20 U/kg demonstrated clear efficacy

relative to Placebo in terms of a significant reduction in the time to onset of symptom relief. The study also demonstrated that Berinert is effective in achieving complete resolution of HAE symptoms within 24 hours in the majority of subjects

Study CE1145_3003 was an uncontrolled, open label, extension study of CE1145_3001. The results confirmed that Berinert is effective in achieving a rapid onset of relief of HAE symptoms in subjects suffering from various types of HAE attacks and in achieving complete resolution of HAE symptoms within 24 hours in the majority of subjects. As Study CE1145_3003 assessed the potential of Berinert for treatment of multiple, subsequent HAE attacks of any type, persistence of efficacy could be demonstrated for time to onset of relief and complete resolution of HAE symptoms.

Study 7D-201CI-OB was an open-label, uncontrolled study that investigated the efficacy and safety of CE1145 in 9 subjects with HAE (7 female, 2 male) after treatment with 20 doses of CE1145 (17 x 500 U, 3 x 1000 U). A total of 8 subjects (16 doses) were treated for edema attacks, and 1 subject (4 doses) was treated prophylactically. The dose range was approximately 6 to 15 U/kg bw for the treatment of attacks and approximately 10 to 20 U/kg bw for the prophylactic treatment. Berinert was effective in treatment and prevention of attacks.

Study CE1145_6001 was a retrospective case collection study in which the efficacy and safety of CE1145 were documented for 20 women who had been treated with CE1145 during pregnancy. A total of 20 pregnant women were included in the analysis, with the observation period for each woman extending for the entire period of the pregnancy. These women had a total of 33 deliveries involving 34 children. Before becoming pregnant, 18 of these subjects had been treated with CE1145 (500, 750, or 1,000 U/attack) and 2 subjects had not been treated with CE1145. During the documented pregnancies, all subjects received CE1145 (500 to 3,500 U/attack). Berinert was effective in all subjects. There were no adverse effects with the use of Berinert in the pregnant women, and no harmful effects on the developing fetuses.

Subjects undergoing extracorporal circulation:

Study 7A-202CH-B was a placebo-controlled, double-blind study that investigated the efficacy and safety of CE1145 in 30 subjects undergoing extracorporeal circulation (randomized 1:1 to CE1145 or Placebo [human albumin 1.1%]). CE1145 was administered as a single i.v. bolus dose of 3,500 U, corresponding to a range of 38.5 to 58.3 U/kg bw. No adverse events related to study drug were reported. The substitution with C1 INH may be useful in patients with both low preoperative C1 INH plasma levels and an insufficient cardiac performance.

Study 7B-201CH-C was a placebo-controlled, double-blind study that investigated the efficacy and safety of CE1145 in 30 subjects undergoing extracorporeal circulation after cardiac surgery (randomized 1:1 to CE1145 or Placebo [human albumin 1.1%]). CE1145 was administered as a single i.v. bolus dose of 2,500 U before heparin administration. In addition, 1 U of CE1145 was given per mL of filling volume. Finally, 1,000 U of CE1145 were administered after neutralization of heparin.

Viral safety studies:

Two earlier, open-label, case documentation studies conducted in 13 subjects with hereditary or acquired C1-INH deficiency were specifically designed to investigate viral safety after single administration of CE1145 (Study 7MN-402CI-OB) and multiple administration of CE1145 (Study 7MN-401CI-OB, involving long-term follow-up of subjects treated in Study 7MN-402CI-OB). No proven case of virus transmission was observed in the study.

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, pregnant or lactating females is limited, although small numbers in clinical trials and publications suggest that the benefit is similar.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions	May occur with use of Berinert, and range from mild (rashes) to severe (shock with fatal outcome)	**Do NOT use Berinert:** if you are hypersensitive (allergic) to the protein C1-esterase inhibitor or any other ingredients of Berinert Please inform your doctor or pharmacist if you are allergic to any medicine or food. **Take special care with Berinert:** if you have experienced allergic reactions to Berinert in the past. You should take antihistamines and corticosteroids prophylactically if advised by your doctor. when allergic or anaphylactic-type reactions occur (a serious allergic reaction that causes severe difficulty in breathing or dizziness). The administration of Berinert

Risk	What is known	Preventability
		should then be stopped immediately (e.g. discontinue infusion) □ if you suffer from laryngeal swelling (laryngeal oedema). You should be carefully monitored with emergency treatment in stand-by. □ during unlicenced use beyond the approved indications and does. Your doctor will consider carefully the benefit of treatment with Berinert compared with the risk of these complications.
Thrombosis or blood clots	Are not common but when they occur, usually occur in patients with other risk factors. These may affect the arteries or veins. In the veins this may lead to a painful swelling of the legs (deep vein thrombosis) and very occasionally 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 with cancer who are being treated with oestrogen are already at higher risk of blood clots so it is difficult to assess what extra risk is caused by Berinert.	Tell your doctor if you have a history of blood clots, or take blood thinners for any reason. **Taking other medicines** □ Please tell your doctor or pharmacist if you are taking or have recently taken any medicines, including medicines obtained without a prescription.
Lack of efficacy	No medicine is 100% effective. Over time, antibodies may develop which make Berinert less effective, or higher doses	Tell your doctor if symptoms are recurring more often or getting more severe.

Risk	What is known	Preventability
	may be needed.	

Important potential risks

Potential Risk	What is known	Preventability
Transmission of infections, such as viruses	When medicines are made from human blood or plasma, certain measures are put in place 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.	Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products. It is strongly recommended that every time that Berinert is given, the date of administration, the batch number and the injected volume should be recorded.
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).	If you think that your doctor is prescribing this drug for other reasons, or if you think that you do not have HAE, discus the condition or disease with the doctor further.

Important missing information

Risk	What is known
Limited information in pregnancy and lactation	**Pregnancy and breast-feeding** If you are pregnant or breast-feeding, please ask your doctor or pharmacist for advice before taking any medicine. During pregnancy and breast-feeding Berinert should be given only if it is clearly needed.
Limited information in children	Available information suggests no differences in children than the adults studies in clinical trials
Limited information in the older population	Available information suggests no differences in children than the adults studies in clinical trials

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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 (PL). The measures in these documents are known as routine risk minimization measures.
This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Patient Registry: CE1145_5002 A multicenter, open, uncontrolled, structured collection of both prospective and retrospective data from patients treated with	The objective of this patient registry is enhanced (active) surveillance of the safety of CSLB C1-INH in clinical practice and to	AEs including thrombotic and thrombo-embolic events and occurrence of suspected viral transmission. Concomitant medications and	Started	Submission of interim data by December 2013 Submission of final data by April 2015

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Berinert. Exposure: 250	facilitate discovery and reporting of adverse events (AEs) including thrombotic events (TE) and potential viral transmissions	plasma products, including reason(s) for administration.		
CE1145_4001 Prospective open-label uncontrolled multi-center post-marketing study to assess inhibitory antibody formation in subjects with congenital C1-INH deficiency and acute hereditary angioedema (HAE) attacks treated with Berinert	Primary Objective: To document the formation of inhibitory anti-C1-esterase-inhibitor (anti-C1-INH) antibodies in subjects with HAE treated with Berinert. Secondary Objective: To document the safety of Berinert in subjects with HAE treated with Berinert. Exploratory Objective: To document the efficacy of Berinert in subjects with HAE treated with Berinert for all types of HAE attacks, and to compare	Development of inhibitory antibodies, AEs, Laboratory safety parameters (hematology, blood chemistry, and urinalysis) Vital signs.	Started	Expected to be completed in 2017

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	efficacy in subjects with and without anti-C1-INH antibodies.			

None of the above studies is a condition of the marketing authorisation in the EU. As post marketing requirements of the marketing authorization in the United States, CSL Behring committed to establishing and maintaining a registry for patients treated with Berinert for any indication (CE1145_5002) and a study to assess inhibitory antibody formation against C1-Esterase Inhibitor in at least 40 patients (CE1145_4001).

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 10: 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 **Important missing information** Limited experience in pregnancy/lactation Limited experience in paediatric 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, as it is a class effect and at request of PEI Off-label use was added as a potential risk, at the request of Health Canada	No additional risk minimization activities were required.