VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

HAE is a rare inherited disorder characterised by recurrent episodes of the accumulation of fluids outside of the blood vessels, blocking the normal flow of blood or lymphatic fluid and causing rapid swelling of tissues in the hands, feet, limbs, face, intestinal tract, or airway. These symptoms develop as the result of deficiency or improper functioning of certain proteins that help to maintain the normal flow of fluids through very small blood vessels (capillaries). The severity of the disease varies greatly among affected individuals. The most common form of the disorder is HAE type I, which is the result of abnormally low levels of certain complex proteins in the blood (C1 esterase inhibitors), known as complements. HAE type II, a more uncommon form of the disorder, occurs as the result of the production of abnormal complement proteins.

VI.2.2 Summary of Treatment Benefits

C1 inhibitor (C1 INH) is a normal constituent of human blood. HAE is also known as C1 INH (C1 INH) deficiency. Administration of CINRYZE increases plasma levels of C1 INH activity and temporarily restores the natural regulation of the complement proteins thereby controlling swelling and preventing swelling.

Clinical studies have demonstrated that treatment with CINRYZE within 4 hours after the onset of an HAE attack resulted in a greater than 2-fold decrease of the symptoms associated with a HAE attack compared to placebo. Use of CINRYZE (compared with placebo) for prevention of HAE attacks, dosed at 1000 Units every 3-4 days, decreased angioedema attack frequency significantly in patients studied.

VI.2.3 Unknowns Relating to Treatment Benefits

The safety population examined during the pre- and post- approval studies of CINRYZE consisted primarily of Caucasian (white) patients. Non-Caucasian patients were not very well represented in the safety population. It is not believed that different ethnic groups would react differently to CINRYZE because C1 INH is a human plasma protein not which is not subject to metabolism by the liver, excretion or drug interactions, however this remains missing information.

It appears from pre-approval studies that children less than 12 years old benefit from the same dosing and frequency as adults. Data from post-approval studies in children also support this theory. In one of the study conducted in children 6-11 years both 500 U (lower dose than in adults) and 1000 U (same dose as in adults) of CINRYZE administered every 3 or 4 days were shown to be effective in the prevention of HAE attacks. A child with severe HAE attacks may require as much, or more, CINRYZE than an adult with less severe disease. However, this remains theoretical and is thus an “unknown”.

VI.2.4 Summary of Safety Concerns

Table 1: Important Identified Risks

Risk	What is Known	Preventability
Thrombosis with high doses	Among other effects in regulation of the complement proteins, C1 INH also regulates the blood clotting system. Because C1 INH inactivates factor XIIa and kallikrein, both of which are activators of the blood clotting system, administration of C1 INH theoretically could have blood coagulation effects. In clinical practice, blood clots have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving high dose C1 INH products other than CINRYZE to prevent blood capillary leak syndrome. The amount of drug given to these infants (up to 500 Units/kg) was significantly greater than that recommended for CINRYZE (1000 Units, equivalent to ~14 Units/kg in a 70 kg person), and was administered to a patient population that did not have C1 INH deficiency. Therefore, the relevance of these data to the use of CINRYZE in subjects with C1 INH deficiency is unknown.	CINRYZE is available as a medicinal product subject to restricted medical prescription.
Thrombosis in patients with thrombogenic risk factors	Thrombosis (blood clots) or other thromboembolic events may occur in patients who are at a higher risk of developing blood clots, including patients with indwelling catheters, known clotting syndromes, obesity, inactivity, cancer, cardiac disease, tobacco smoking, high pressure and high cholesterol. Treatment of patients with CINRYZE who have thrombotic risk factors would only occur after full consideration of the risk/benefit analysis for the patient.	CINRYZE is available as a medicinal product subject to restricted medical prescription.
Hypersensitivity reactions	Patients who are treated with human plasma proteins may experience immune responses which could result in	CINRYZE is available as a medicinal product subject to restricted medical prescription.

Table 1: Important Identified Risks

Risk	What is Known	Preventability
	hypersensitivity reactions e.g. mild skin rashes or potentially more serious anaphylactic reactions. However a hypersensitivity reaction is expected to be infrequent as CINRYZE is a naturally occurring human plasma protein typically not recognised as a foreign antigenic epitope by a patient's immune system. Some patients who have an autoimmune disease or lymphoproliferative syndrome may develop antibody to C1 INH.	
Development of C1INH antibodies	CINRYZE is manufactured from human blood plasma. Patients who are treated with human blood plasma proteins have the potential to develop an antibody response. However, in over 30 years of clinical experience with human-derived C1 INH products, anti-C1 INH antibody formation appears to have been reported only in relation to autoimmune disease and not due to treatment with this plasma protein.	CINRYZE is available as a medicinal product subject to restricted medical prescription.
Adverse events with self or home administration of CINRYZE	There is potential for serious side effects to occur with self or home administration, including but not limited to bleeding, local inflammatory reactions, artery puncture, air blocks via indwelling catheters, incorrect administration of heparin (used to stop blood clots) in indwelling catheters, or local infections.	CINRYZE is available as a medicinal product subject to restricted medical prescription.

Table 2: Important Potential Risks

Risk	What is Known (Including reason why it is considered a potential risk)
Transmission of infectious diseases	CINRYZE is manufactured from human blood plasma, and as such, has a theoretical risk for certain infectious disease transmission to other humans. However, donated human blood plasma is screened with highly sensitive assays for human viruses including HIV and certain hepatitis viruses (HAV, HBV, and HCV). Furthermore, the CINRYZE manufacturing process incorporates three virus inactivation/removal steps: polyethylene glycol precipitation, pasteurisation, and nanofiltration to further reduce the possibility of infectious disease transmission.

Table 2: Important Potential Risks

Risk	What is Known (Including reason why it is considered a potential risk)
Medication error	CINRYZE can be administered at home. Potential risks associated with home-treatment are related to the administration itself as well as the identification of certain ADRs, particularly hypersensitivity (as symptoms can be similar to an angioedema attack). Another potential risk associated with home treatment is self-administration of inadequate doses. Very high doses of C1 INH (up to 500 Units/Kg) have been associated with the formation of blood clots inside a vessel (thrombotic events) in neonates; however, such high doses would not typically be achievable with the amount of drug dispensed for prevention of angioedema attacks.

Table 3: Missing Information

Risk	What is Known
Use in children (less than 12 years of age)	CINRYZE has been shown to be effective and well tolerated in children with HAE aged between 2 and 11. The safety profile of CINRYZE has not been characterised in Pre-term newborns, Neonates (birth to 27 days) and in infants and toddlers (28 days to 23 months) as the condition does not typically manifest clinically in these age groups.
Limited information is available for use in pregnancy.	**Pregnancy** Data on a limited number of exposed pregnancies indicate no adverse effects of C1 INH on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. No maternal or embryofoetal effects of treatment were observed in reproductive studies in rats at dose levels up to 28-times the recommended human dose (1000 Units) based on an average adult body weight of 70 kg. The potential risk for humans is unknown. Therefore, CINRYZE should be given to pregnant women only if clearly indicated. **Breast-feeding** It is unknown whether C1 INH is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from CINRYZE therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Fertility** No specific studies on fertility, early embryonic and postnatal development, or carcinogenicity studies were conducted.
Use in non-Caucasian patients	C1 esterase inhibitor becomes biologically inactive after binding to its target and is then is metabolised the same regardless of ethnicity.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising 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 minimisation measures.

The Summary of Product Characteristics and the Package leaflet for CINRYZE ® can be found on the European Medicines Agency (EMA) European Public Assessment Report (EPAR) page. This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in X's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

VI.2.5.1 Safety Concern in Lay Terms (Medical Term)

Risk minimisation measure(s): Educational material for Healthcare Professionals (HCPs) and non-HCPs
Inclusion of key elements in the educational material for HCPs
It is the responsibility of the prescribing physician to determine which patients may be suitable for home or self-administration of CINRYZE ® It is the responsibility of the prescribing physician to provide appropriate training to the non-HCP who will administer the treatment at home, such as the patient for self- administration or a family member. Regular review of the administration by the patient/carer needs to be performed to ensure CINRYZE® is administered correctly and appropriately. It is the responsibility of the prescribing physician to verify that all the necessary skills have been acquired by the non-HCP and that CINRYZE® may be safely and effectively administered at home. A leaflet providing detailed information on the key elements of the training that should be kept at home for further reference

VI.2.6 Planned Post Authorisation Development Plan

Table 4: Overview of Ongoing and Planned Studies

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)
0624-301, Phase 3 study (Category 3)	A Phase 3, Multicenter, Randomized, Single-blind, Dose-ranging,Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of CINRYZE ® (C1 Esterase Inhibitor [Human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of Age With Hereditary Angioedema	Assessment of safety, pharmacokinetics and clinical effect of CINRYZE in children	Ongoing	Final study report (planned Nov 2017)
0624-401, Phase 4 PAOS study/ Icatibant Outcome Survey (IOS), Disease Registry for compliance with an Annex II.D condition (Registry) (Category 1)	A European multi-center, multi-country, post-authorisation, observational study (registry) of patients with HAE who are administered CINRYZE (C1 inhibitor [human]) for the treatment or prevention of HAE attacks	To characterise the safety and use of Cinryze in routine clinical practice when administered for (1)routine prevention of angioedema attacks, (2) pre-procedure prevention of angioedema attacks, and/or (3) treatment of angioedema attacks. To monitor severe attacks and laryngeal attacks, as well as cases in which treatment with CINRYZE is initiated more than 4 hours after onset of an attack.	Ongoing*	With PSUR submissions

*Enrolment in the 0624-401 study is complete. Patients who completed participation in 0624-401 can be enrolled in IOS disease registry, if they consent

VI.2.6.1 Studies which are a Condition of the Marketing Authorisation.

There is no current planned post authorisation development plan.

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

Table 5: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	02SEP2009	Not Applicable	Original Version
2.0	25FEB2010	No changes to safety concerns	
3.0	10SEP2010	No changes to safety concerns	MAA module changes due to Day 120 responses
4.0	12JAN2011	No changes to safety concerns	MAA module changes due to Day 180 responses
5.0	21FEB2011	No changes to safety concerns	Changes due to label changes for EMA approval, updated patient number projections
6.0	10MAR2011	No changes to safety concerns	Changes due to label changes for EMA approval and RMP Summary table
7.0	16MAR2011	No changes to safety concerns	Addition of date of CSR for 0624-400 study
8.0	31AUG2011	No changes to safety concerns	Addition of post marketed information
9.0	14FEB2014	Hypersensitivity added as a potential risk	Updated to modular format, potential risk addition (detailed in previous versions).
10.0 10.1 10.2	26MAY2016 03NOV2016 14DEC2016	Off-label use deleted as potential risk	Updates reflect changes due to pediatric indication