EU RISK MANAGEMENT PLAN (RMP)

for

CINRYZE (Human C1 Esterase inhibitor)

RMP Version number: 11.2

Date: 31-March-2025

[redacted]

[redacted]

EU Risk Management Plan for CINRYZE (Human C1 Esterase inhibitor)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 11.2

Data lock point for this RMP: 24-October-2024

Date of final sign off: 31-March-2025

Rationale for submitting an updated RMP: To address the request for supplementary information included in the Type II variation assessment report of procedure EMEA/H/C/001207/II/0104, dated 13-February-2025, the Risk Management Plan (RMP) is being amended to update the missing information as "Use in children less than 6 years of age" from "Use in children less than 2 years of age".

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Updated with latest Summary of Product Characteristics (SmPC).
Part II Safety Specification	
– **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable
– **Module SII Non-clinical part of the safety specification**	Not applicable
– **Module SIII Clinical trial exposure**	Not applicable
– **Module SIV Populations not studied in clinical trials**	Not applicable
– **Module SV Post-authorisation experience**	Not applicable
– **Module SVI Additional EU requirements for the safety specification**	Not applicable
– **Module SVII Identified and potential risks**	Missing information "Use in children less than 2 years of age" is updated as "Use in children less than 6 years of age".
– **Module SVIII Summary of the safety concerns**	Missing information "Use in children less than 2 years of age" is updated as "Use in children less than 6 years of age".
Part III Pharmacovigilance plan	Not applicable
Part IV Plans for post-authorisation efficacy studies	Not applicable

[redacted]

RMP Module:	Significant Changes:
Part V Risk minimisation measures	Missing information "Use in children less than 2 years of age" is updated as "Use in children less than 6 years of age".
Part VI Summary of the risk management plan	Updates made in line with Part II and Part V.
Part VII Annexes	Annex 8 was updated to present the changes made from v11.1 to 11.2.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 11

Approved with procedure: EMEA/H/C/001207/IB/0099

Date of approval (opinion date): 31-October-2023

QPPV name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by [redacted] Deputy EUQPPV [redacted], on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: Signatures are available on file.

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List of Abbreviations

Abbreviation	Definition/Description
ACE	Angiotensin-Converting Enzyme
ADR	Adverse Drug Reaction
AMR	Antibody-Mediated Rejection
ATC code	Anatomical Therapeutic Chemical classification system
C1 INH	Human C1-esterase Inhibitor
DLP	Data Lock Point
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FFP	Fresh frozen plasma
HAE	Hereditary Angioedema
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCP	Healthcare Professionals
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICSR	Individual Case Safety Report
INN	International Non-proprietary Names
IU	International Units
IV	Intravenous
Kg	Kilogram
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
NOAEL	No Observed Adverse Effect Level
pdC1 INH	Plasma-Derived C1 INH Concentrates
PEG	Polyethylene Glycol
PIP	Paediatric Investigation Plan
PY	Patient Years
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
RMP	Risk Management Plan
RSI	Reference Safety Information
SLE	Systemic Lupus Erythematosus

[redacted]

Abbreviation	Definition/Description
SmPC	Summary of Product Characteristics

[redacted]

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Human C1-esterase inhibitor (C1 INH)
Pharmacotherapeutic group(s) (ATC Code)	Drugs used in hereditary angioedema (B06AC01)
Marketing Authorisation Holder	Takeda Manufacturing Austria AG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	CINRYZE®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Serine protease inhibitor
	Summary of mode of action: C1-esterase inhibitor inhibits the complement system by binding C1r and C1s, two of the active enzyme subunits of the first component of the complement system (C1) in the classical pathway, as well as to mannose binding lectin associated serine proteases in the lectin pathway. The primary substrate of the activated C1 enzyme is C4; uninhibited C1 results in diminished C4 levels. C1 is the most important inhibitor of contact activation and regulates the contact system and the intrinsic coagulation pathway by binding to and inactivating kallikrein and factor XIIa. Because these pathways are part of enzyme amplification cascades, without C1-esterase inhibitor, spontaneous or trigger induced activation of these pathways can lead to unopposed activation and oedematous swelling.
	Important information about its composition: Each single-use powder vial contains 500 International Units (IU) of Human C1-esterase inhibitor produced from the plasma of human donors. After reconstitution, one vial contains 500 IU of Human C1-esterase inhibitor per 5 mL corresponding to a concentration of 100 IU/Ll. One IU is equivalent to the amount of C1-esterase inhibitor present in 1 mL of normal human plasma. The total protein content of the reconstituted solution is 15 ± 5 mg/mL. *Excipient with known effect:* Each vial of CINRYZE contains approximately 11.5 mg of sodium.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current: • Treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE).

[redacted]

<table>
<tr><td></td><td>• Routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
<u>Adults</u>
<u>Treatment of angioedema attacks</u>
• 1,000 IU of CINRYZE at the first sign of the onset of an angioedema attack.
• A second dose of 1,000 IU may be administered if the patient has not responded adequately after 60 minutes.
• For patients experiencing laryngeal attacks or if initiation of treatment is delayed, the second dose can be given sooner than 60 minutes.
<u>Routine prevention of angioedema attacks</u>
• 1,000 IU of CINRYZE every 3 or 4 days is the recommended starting dose for routine prevention against angioedema attacks; the dosing interval may need to be adjusted according to individual response. The continued need for regular prophylaxis with CINRYZE should be reviewed on a regular basis.
<u>Pre-procedure prevention of angioedema attacks</u>
• 1,000 IU of CINRYZE within 24 hours before a medical, dental, or surgical procedure.
<u>Paediatric population</u>
Adolescents: For treatment, routine prevention and pre-procedure prevention in adolescents 12 to 17 years old, the dose is the same as for adults.
Children: The safety and efficacy of CINRYZE in children less than 2 years old has not been established and data supporting dosing recommendations in children less than 6 years old are very limited.
<table>
<tr><td>Treatment of angioedema attacks</td><td>Pre-procedure prevention of angioedema attacks</td><td>Routine prevention of angioedema attacks</td></tr>
<tr><td><u>2 to 11 years, >25 kg:</u>
1,000 IU of CINRYZE at the first sign of the onset of an acute attack.
A second dose of 1,000 IU may be administered if the patient has not responded</td><td><u>2 to 11 years, >25 kg:</u>
1,000 IU of CINRYZE within 24 hours before a medical, dental, or surgical procedure.</td><td><u>6 to 11 years:</u>
500 IU of CINRYZE every 3 or 4 days is the recommended starting dose for routine prevention against angioedema attacks. The dosing interval and dose may need to be</td></tr>
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</td></tr>
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	adequately after 60 minutes.		adjusted according to individual response. The continued need for regular prophylaxis with CINRYZE should be reviewed on a regular basis.
	2 to 11 years, 10-25 kg: 500 IU of CINRYZE at the first sign of the onset of an acute attack. A second dose of 500 IU may be administered if the patient has not responded adequately after 60 minutes.	*2 to 11 years, 10-25 kg:* 500 IU of CINRYZE within 24 hours before a medical, dental, or surgical procedure.	
	Elderly patients: No special investigations have been performed. For treatment, routine prevention and pre-procedure prevention in elderly patients, 65 years of age or older, the dose is the same as for adults. *Patients with renal or hepatic impairment:* No special investigations have been performed. For treatment, routine prevention and pre-procedure prevention in patients with renal or hepatic impairment, the dose is the same as for adults. *Method of administration* • For intravenous use only. • The reconstituted product should be administered by intravenous injection at a rate of 1 mL per minute.		
	Proposed: Not applicable.		
Pharmaceutical form(s) and strengths	Current: Powder and solvent for solution for intravenous injection. Each lyophilized powder vial contains 500 IU of Human C1-esterase inhibitor produced from the plasma of human donors. After reconstitution, one vial contains 500 IU of Human C1-esterase inhibitor per 5 mL, corresponding to a concentration of 100 IU/mL. Two vials of reconstituted CINRYZE contain 1,000 IU of Human C1-esterase inhibitor per 10 mL, corresponding to a concentration of 100 IU/mL. One IU is equivalent to the amount of Human C1-esterase inhibitor present in 1 mL of normal human plasma.		
	Proposed: Not applicable.		
Is/will the product be subject to additional monitoring in the EU?	No		

[redacted]

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Hereditary Angioedema (HAE)	
Incidence:	Not applicable.
Prevalence:	The minimum estimated prevalence of diagnosed cases of hereditary angioedema types 1 and 2 (C1 INH-HAE), is approximately 1.5 per 100,000 (or ~1 in 67,000) based on a systematic review of studies from 6 European countries [redacted]. The estimated minimum prevalence in the Asia Pacific region is 0.02 per 100,000 [redacted]. The true prevalence is assumed to be higher due to undiagnosed cases. A study of asymptomatic or undiagnosed family members of people with HAE found that 30% met the diagnostic criteria for HAE [redacted]. Type 1 is the most common type (91%), followed by type 2 (9%) [redacted].
Demographics of the target population in the indication:	HAE is slightly more common in females (56%) [redacted]. No differences in race and ethnicity have been reported [redacted]. The SERPING1 mutation for C1 INH-HAE type 1 and 2 is present at birth, but symptoms are uncommon in neonates and infants. Disease presentation can occur at any age, but usually begins in childhood or adolescence. In the Global HAE Registry, the median age at diagnosis was 23 years (range 8-80) [redacted]. Approximately 50% experienced initial symptoms before the age of 12 years, and 90% by 25 years of age.
Risk factors for the disease:	The genetic risk factor for C1 INH-HAE (types 1 and 2) is a mutation of the SERPING1 gene, which codes for C1 INH. C1 INH-HAE is a rare autosomal dominant disease (i.e., offspring of people with C1 INH-HAE have a 50% chance for inheritance). Risk factors for unfavourable outcomes and acute events include: delays in diagnosis, misdiagnosis, young adult age, dental procedures, endoscopy or intubation, absence of long-term prophylaxis when indicated, and lack of knowledge about HAE by patients and emergency physicians [redacted]. Estrogen replacement therapy and angiotensin-converting enzyme (ACE) inhibitors can significantly increase the frequency and severity of HAE attacks [redacted]. In women, menstruation, ovulation, pregnancy, and lactation can also serve as attack triggers [redacted]. Gender, BMI, alcohol, or smoking do not appear to impact HAE severity [redacted].
The main existing treatment options:	For long-term prophylaxis, first-line therapies include plasma-derived C1 INH concentrates (pdC1 INH), lanadelumab, or berotralstat [redacted]. Androgens are considered second-line treatment; yet remain widely used [redacted]. Antifibrinolytics such as tranexamic acid are not recommended for long-term prophylaxis. Short-term prophylaxis with pdC1 INH, androgens, and recombinant human C1 INH may be prescribed in advance of upcoming triggers [redacted]. Fresh frozen plasma (FFP) maybe administered if insufficient time for other options. Rescue (on-demand) treatments for attacks include intravenous (IV) C1 INH, ecallantide, and icatibant [redacted]. Recent treatment guidelines recommend pdC1 INH as the preferred

Hereditary Angioedema (HAE)	
	therapy during pregnancy and lactation [redacted]. In children under 12 years, C1 INH or icatibant are recommended for treatment of attacks. Ecallantide is licensed for the use in adolescents in the US. The preferred therapy in children younger than 12 years of age for long-term prophylaxis is pdC1 INH.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	HAE is characterised by attacks of edema in the extremities, face, tongue and larynx, abdomen, and genitalia, ranging from mild to severe. The most common affected area is the abdomen and skin [redacted]. Abdominal symptoms, prior to HAE diagnosis, can result in unnecessary surgeries and medical procedures [redacted]. Annually, the number of attacks varies widely. Patients enrolled in a survey in Japan had an average of 15.7 (range 0-100) attacks per year, with 53.1% requiring treatment [redacted]. Patients participating in a US survey had an average of 26.9 attacks per year, 28.4% of which were severe [redacted]. Laryngeal edema leading to asphyxiation accounts for most HAE deaths. A systematic review found between 33% and 56% of patients with HAE died due to laryngeal edema, with an average mortality rate of 1:20 (range: 1:120 - 1:2) [redacted]. Approximately 50% experienced laryngeal edema at least once in their lifetime. In a Chinese cohort of 103 therapy-free patients, the median annual frequency of laryngeal edema was 0.5 per year with approximately one-half requiring emergency care [redacted]. The median age at death due to laryngeal edema was 46 (IQR 35-53) years. HAE may worsen with increasing age until approximately 50 years of age or older. Nearly half of a Chinese cohort experienced their first attack during puberty, and one-third during their twenties [redacted]. The disease remained relatively severe until age 50 years. Beyond 50 years of age, it appears to decrease in severity [redacted]. Delays in diagnosis are common, ranging from 8 to 16 years from first symptoms to HAE diagnosis [redacted]. In a large, multinational observational study, 44.3% of patients with HAE had at least 1 prior misdiagnosis [redacted]. In a German study, 49.4% of patients reported a misdiagnosis; and of those, 80% reported incorrect treatment [redacted]. Misdiagnosis was a major driver of diagnostic delays. Most (71%) of the HAE attacks occurred in patients who were not on prophylactic medication.
Important co-morbidities:	Co-morbidities associated with C1 INH-HAE (type 1 and 2) include [redacted]: • Cardiovascular diseases, primarily, arterial and venous thrombosis/embolus and hypertension • Autoimmune diseases, primarily, systemic lupus erythematosus (SLE), autoimmune endocrine disease, and musculoskeletal and connective tissue disorder (e.g., rheumatoid arthritis, psoriatic arthritis) • Allergy, asthma, atopic dermatitis • Anxiety and depression [redacted]

[redacted]

Part II: Module SII - Non-clinical part of the safety specification

The development program for CINRYZE includes a comprehensive series of non-clinical pharmacology, pharmacokinetic, and toxicology studies that support the safety of the product for the intended single-dose IV use. In particular, the results of the acute and repeat-dose toxicity studies and the 7– and 14–day repeat-dose studies in rats, the embryo-foetal toxicity studies in rats, evaluation of an earlier generation product of C1 INH in a rabbit safety pharmacology model, the special studies to evaluate if the pasteurisation step in the manufacture of C1 INH (C1 INH-HP) which causes the formation of neo-epitopes on the C1 INH proteins, indicates that there are no adverse systemic effects that would preclude the intended IV clinical use of CINRYZE.

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	**Relevance to human usage**
Toxicity:	
Single and Repeat-dose Toxicity Acute and repeat-dose toxicity studies were performed in rats with IV administration of CINRYZE at dose levels of 20, 100, or 400 IU/kg. No signs of toxicity were observed in the single-dose study up to 400 IU/kg, which was the highest dose tested. In the repeat-dose toxicity study, the signs of toxicity were limited to minor increases in inflammatory changes in the lungs and germinal center hypertrophy in the spleen in animals dosed at 400 IU/kg for 14 days, as compared to control animals. The effects in the lungs are quite common in rats following IV administration. Although the extent of effects was deemed to be equivocal, it cannot be excluded that it was caused by C1 INH. The amount of germinal center hypertrophy in the spleens of rats treated at 400 IU/kg was within the normal background histopathology range, in both incidence and severity, but did correlate with a small increase in spleen weight at this dose level and may have been a reflection of the inflammatory changes in the lungs.	The single and repeat-dose no-observed-adverse-effect-level (NOAEL) of CINRYZE is considered to be 400 IU/kg, which was the highest dose tested and is representing a 24-fold margin over the highest single clinical dose.
Reproductive and Developmental Toxicity Animals were dosed from Gestation Day 6 until Gestation Day 17 (included) and euthanised on Gestation Day 20 and the status of each implantation was recorded. There were no clinical observations during the treatment period or necropsy findings that were considered to be related to treatment. Mean body weight gains and food consumption were similar in all groups. Pregnancy performance values were similar in all groups. Under the conditions of the definitive study, 400 IU/kg/day was identified as the NOAEL for both maternal and fetal effects.	No effects on embryo-foetal development were observed at dose levels up to 400 IU/kg. No animal studies have been completed to evaluate the effects of CINRYZE on the impairment of fertility.

[redacted]

Key Safety Findings	Relevance to human usage
Nephrotoxicity	C1 INH is an endogenous human plasma protein which is metabolised and degraded to small peptides and individual amino acids. The pharmacokinetics and excretion of C1 INH are not expected to be altered by the presence of renal or hepatic impairment.
Hepatotoxicity	
Genotoxicity	No animal studies have been completed to evaluate the effects of CINRYZE on mutagenesis.
Carcinogenicity	
Mechanisms for Drug Interactions	C1 INH is an endogenous human plasma protein which is not subject to metabolism by cytochrome P450 iso-enzymes. Drug-drug interactions are not expected.
Other Toxicity-related Information or Data	Evaluation of an earlier generation product of C1 INH in a rabbit safety pharmacology model identified a potential thrombogenic threshold at doses greater than 200 Units/kg (approximately 14 times the recommended adult clinical dose of CINRYZE). An immunogenicity study with C1 INH-HP in rabbits determined that pasteurisation during the manufacturing process did not result in the formation of neo-epitopes on the C1 INH protein.

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Duration of exposure

Cumulative Estimated Subject Exposure in LEVP Pharmaceuticals Inc., Clinical Studies		
Total Exposed Population		
	Number of subjects*	**Clinical Trial Number**
1,000 Units IV per dose C1 INH	71	LEVP 2005-1/A
1,000 Units IV per dose C1 INH	113	LEVP 2006-1
1,000 Units IV every 3-4 days C1 INH	25	LEVP 2005-1B
1,000 Units IV every 3-7 days C1 INH	146	LEVP 2006-4
1,000 Units IV (1 dose vs. 2 doses) C1 INH	27	LEVP 2006-5
1,000 Units IV per dose C1 INH**	3	LEVP 2006-2, 2005-4 and 2005-3
CI INH Total	**385**	

*All subjects had HAE. Subjects may have participated in multiple studies. Therefore, there have been 262 unique subjects exposed 46 of which were children aged 2-5 years old (n=3), 6-11 (n=17) and 12-17 (n=26) years of age.

**One patient each in three compassionate use trials.

Cumulative Subject Exposure to C1 INH in ViroPharma and Shire Clinical Studies		
Treatment	**Number of subjects**	**Clinical Trial Number**
HAE		
2,000* U IV, 2,000 U SC	9	0624-100
1,000** U IV, 1,000 U SC, 2,000 U SC	26	0624-103
1,000 U IV, 1,000 U SC, 2,000 U SC	26	0624-200
500 U, 1,000 U, or 1,500 U IV	9	0624-203
1,000 U IV	8	0624-209
2,000 U SC	71	SHP616-300
500 U, 1,000 U IV	12	0624-301
1,500 U, 2,000 U, 2,500 U IV	20	0624-400
Antibody-mediated rejection (AMR) in Kidney Transplantation		
5,000 U, 2,500 U IV	20	SHP616-302
5,000*** U, 2,500 U	9	0624-201
Total (C1 INH)	210	

*One subject in 0624-100 served as a sentinel subject to evaluate local tolerability of a SC injection of

Cumulative Subject Exposure to C1 INH in ViroPharma and Shire Clinical Studies		
Treatment	**Number of subjects**	**Clinical Trial Number**
CINRYZE. This subject received a single 1.5 mL SC injection of CINRYZE (500 U), and a single 1.5 mL SC injection of isotonic saline injected at 2 separate sites in the abdomen. **1,000 U IV doses were administered with the commercial CINRYZE lyophilized powder formulation. 1,000 U SC and 2,000 U SC doses were administered with C1 esterase inhibitor [human] liquid for injection formulation. ***0624-201 was investigating the use of higher dose C1 INH for the treatment of AMR in kidney transplantation CINRYZE 5,000 U (Day 1); CINRYZE 2500 U (Days 3, 5, 7, 9, 11, and 13). Total dose is 20,000 U over 13 days. Note: Dosage and routes of administration (IV=intravenous; SC=subcutaneous) differed by clinical trial. Therefore, this table is presented by clinical trial exposure. Patients and healthy volunteers are included as of 15-June-2022.		

Number of subjects	LEVP studies	ViroPharma/Shire studies	Total
Number of subjects enrolled	385	242*	**627**
Number of unique subjects exposed to C1 INH	262	210	**472**
*Includes 32 patients who received placebo.			

Table SIII.2: Age group and gender

Cumulative Exposure to C1 esterase inhibitor (human) from Completed ViroPharma and Shire Clinical Studies Presented by Age and Sex			
Age Range (years)	**Male**	**Female**	**Total**
<18 years	11	18	29
18-65	71	100	171
66-75	5	4	9
≥75	0	1	1
Total	**87**	**123**	**210**

Table SIII.3: Ethnic origin

Cumulative exposure to C1 esterase inhibitor (human) From ViroPharma and Shire clinical studies presented by ethnic origin	
Ethnic origin	**Number of subjects**
Asian	10
Black	19
Native Hawaiian or Other Pacific Islander	2

[redacted]

Cumulative exposure to C1 esterase inhibitor (human) From ViroPharma and Shire clinical studies presented by ethnic origin	
Caucasian	174
Other	5
Total	**210**

Part II: Module SIV - Populations not studied in clinical trials

The following patient groups were excluded from the clinical studies of CINRYZE for HAE subjects with low C1 level, B cell malignancy, presence of anti-C1 INH autoantibody, subjects with any clinically significant medical condition such as renal failure, subjects who were pregnant and breast-feeding, history of hypercoagulability (abnormal blood clotting), history of allergic reaction to C1 INH products, including CINRYZE (or any of the components of CINRYZE), or other blood products, known allergy to hyaluronidase or any other ingredient in the study formulation, known hepatitis B or C infection, known immune deficiency disease or was positive for human immunodeficiency virus (HIV).

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

History of allergic reaction to C1 INH products, including CINRYZE (or any of the components of CINRYZE)	
Reason for exclusion:	Patients with known hypersensitivity to CINRYZE or any of the excipients or to C1 INH products should not receive CINRYZE.
Is it considered to be included as missing information?:	No.
Rationale:	As with any product, hypersensitivity reactions are possible. Hypersensitivity is an important identified risk with the product. Hypersensitivity also remains a contraindication for use. Patients with hypersensitivity to the active substance or to the excipients should avoid using the product.

History of hypercoagulability (abnormal blood clotting)	
Reason for exclusion:	Among the regulatory effects of the complement and contact pathways, C1 INH also regulates the fibrinolytic system. Because C1 INH inactivates plasmin, an activator of fibrinolysis, administration of C1 INH theoretically could have pro-coagulatory effects. In clinical practice, thrombotic events have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving off-label high dose C1 INH products other than CINRYZE to prevent capillary leak syndrome. The dosing regimen in these infants (up to 500 IU/kg) was significantly greater than that recommended for CINRYZE (1,000 IU, equivalent to ~14 IU/kg in a 70 kg person) and was administered to a patient population that did not have congenital C1 INH deficiency. Thus, the relevance of these data to the use of CINRYZE in subjects with congenital C1 INH deficiency is unknown. Nevertheless, ViroPharma conducted a Phase 4 dose-escalation study, that addressed the risk for thrombotic or thromboembolic events (as prospectively defined in the protocol) as any occurrence of these events were tracked through mandatory safety reporting. There were no systemic thrombotic events in subjects of that study dosed as high as 2,500 IU twice weekly.

History of hypercoagulability (abnormal blood clotting)	
Is it considered to be included as missing information?:	No.
Rationale:	Thrombosis with high doses is an important identified risk with the use of the product.

Presence of anti-C1 INH autoantibody	
Reason for exclusion:	Patients with autoantibody, as occurs in lymphoma or in certain autoimmune disease such as SLE multiple myeloma or monoclonal gammopathy of undetermined significance may not respond to CINRYZE administration for alleviation of angioedema attacks.
Is it considered to be included as missing information?:	No.
Rationale:	Development of C1 INH antibodies are an important identified risk with the use of the product.

Known hepatitis B or C infection, known immune deficiency disease or was positive for HIV	
Reason for exclusion:	CINRYZE is manufactured from human plasma, and as such, has a theoretical risk for certain infectious disease transmission (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent). However, donated human plasma is screened with highly sensitive assays for human pathogens including HIV and certain hepatitis viruses (hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV)). Furthermore, the CINRYZE manufacturing process incorporates three virus inactivation/removal steps: polyethylene glycol (PEG) precipitation, pasteurisation, and nanofiltration to further reduce the possibility of infectious disease transmission. The clinical development programme specifically tested for HBV, HCV, HIV, and tracked all other infections via mandatory safety reporting. Approximately 14,500 infusions of CINRYZE were administered during the clinical development program leading to market authorisation without any evidence of transmission of infectious disease.
Is it considered to be included as missing information?:	No.
Rationale:	Risk of transmission of infectious diseases is an important potential risk with the use of the product.

[redacted]

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

Ability to Detect Adverse Reactions	Limitation of Study Programme	Discussion of Implications for Target Population
Which are rare	Numbers of patients studied would be limited due to populations excluded from the clinical trial programme and the very limited population with HAE.	Implications to target population with respect to predicting the safety of the product in the marketplace due to populations not studied.
Due to prolonged exposure	Although the open-label prophylaxis study in HAE (LEVP 2006-4) followed some subjects beyond a year, CINRYZE prophylaxis is a lifelong therapy so consequences of longer-term exposure could only be extrapolated.	Implications to target population with respect to predicting the safety of the product for use lifelong could not be predicted, only extrapolated.
Due to cumulative effects	Difficulty in assessing possible cumulative effects, for example specific organ toxicity, could not be assessed from the short-term pivotal studies.	Implications to target population with respect to cumulative effects of the product in the marketplace are not expected since C1 INH is a normal component of human plasma, and it is consumed physiologically leading to no known cases of prolonged supraphysiologic levels.
Which have a long latency	The only known latent events would be those of transmissible hepatitis or prion disease.	The manufacturing process for CINRYZE involves three steps that would eradicate transmissible infectious agents: pasteurization, PEG precipitation, and nanofiltration. The first two steps were utilised in previous C1 INH products which have been available in the marketplace for 30 years. To date, there have been no signals for such infectious disease transmission. CINRYZE manufacturing adds the third step of nanofiltration to provide an even greater assurance of safety.

[redacted]

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	Across all of the clinical studies, there were 61 unique paediatric subjects enrolled and exposed to over 2500 infusions of CINRYZE (2-5 years, n=3; 6-11 years, n= 32; 12-17 years, n=26). Among these children, the only adverse reactions with CINRYZE included headache, nausea, pyrexia, and infusion site erythema. None of these adverse reactions were severe, and none led to discontinuation of study drug. Overall, there were no clinically meaningful adverse trends observed in frequency or types of adverse events (AEs) observed among paediatric subjects compared to adults. No subjects (children) were discontinued from CINRYZE therapy due to an adverse event in any clinical study. Overall, the safety and tolerability of CINRYZE are similar in children (2-5, 6-11, and 12-17 years old) and adults (≥18 years old). 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, or is not diagnosed until a later age, in these subsets.
Elderly	No special investigations have been performed. The SmPC states the following in section 4.2 Posology and method of administration: *Elderly patients* No special investigations have been performed. For treatment, routine prevention and pre-procedure prevention in elderly patients, 65 years of age or older, the dose is the same as for adults.
Pregnant or Breast-feeding women	Across all of the completed clinical studies, there were 15 females enrolled and exposed to CINRYZE who were pregnant or became pregnant during the CINRYZE Clinical Development Program (age groups: 16-45 years). Among these pregnancies, 10 resulted in a healthy birth, one pregnancy resulted in a spontaneous abortion (previous miscarriage and ectopic pregnancy reported), one pregnancy resulted in a stillbirth (multiple congenital anomalies predated the use of CINRYZE, therefore treatment considered not related), and three pregnancy outcomes were unknown. Overall, there were no clinically meaningful adverse trends observed in frequency or types of AEs observed. The SmPC states the following in section 4.6 Fertility, pregnancy and lactation. *Pregnancy* Human C1-esterase inhibitor is a physiological component of human plasma. Therefore, no adverse effects on fertility, pre- and post-natal development are expected in humans. Animal-reproductive studies show no maternal or embryo-foetal effects in rats at dose levels up to 28 times the recommended human dose (1,000 IU) based on an average

Type of special population	Exposure
	adult body weight of 70 kg. Data on a limited number of exposed pregnancies are available from clinical studies and from post-marketing experience (including data from two observational studies) and indicate no adverse effects of Human C1-esterase inhibitor on pregnancy or on the health of the foetus/newborn child. 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 post-natal development, or carcinogenicity studies were conducted.
Patients with Hepatic and renal impairment	C1 INH is an endogenous human plasma protein which is not subject to metabolism by cytochrome P450 iso-enzymes, excretion, or pharmacokinetic drug-drug interactions exhibited by many low molecular weight compounds. The expected consequence of metabolism of a glycoprotein is via degradation to small peptides and individual amino acids. As such, the pharmacokinetics and excretion of C1 INH are not expected to be altered by the presence of renal or hepatic impairment.
Patients with Other Relevant Co-morbidity	This aspect of HAE was not evaluated.
Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Study Population	This aspect of HAE was not evaluated.
Population with relevant different Racial and/or Ethnic Origin	The majority of subjects in the CINRYZE development program for HAE were Caucasian.
Subpopulations carrying relevant genetic polymorphisms	C1 INH is an endogenous human plasma protein which is not subject to metabolism by cytochrome P450 iso-enzymes, excretion, or pharmacokinetic drug-drug interactions exhibited by many low molecular weight compounds. Therefore, inter-ethnic differences in pharmacokinetics of drugs due to types and/or frequencies of gene variants coding for drug metabolising enzymes are of minimal consequence.

[redacted]

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

The methodology used to calculate the exposure assumes two doses (4 vials of 500 International Units [IU]) per week of 2,000 mg based on the current reference safety information (RSI) for routine prevention of angioedema attack. Patient year (PY) is a measure of patient exposure to C1 INH based on the estimated number of patients who could be receiving routine prevention with C1 INH for 1 full year. The calculation of PYs assumes that all distributed doses are used in routine prevention of attacks and that each patient receives 2,000 IU per week or 104,000 IU per year (the number of doses over the course of a full year, or 2,000 IU in 52 weeks).

Commercial data indicate that the average dose per patient for routine prevention is actually 900 IU per week. For instance, if a total of X IU were distributed in a given year, the approximate PYs is X IU divided by 52,000 IU per year.

The consequent underestimate of total exposure using a dosing factor of 2,000 IU versus 900 IU more than compensates for the exclusion of the relatively low number of doses that may be used for few days exposure for acute treatment and pre-procedure prevention of angioedema attacks that are difficult to estimate and integrate into the total exposure estimate.

SV.1.2. Exposure

Based on the above methodology, cumulative global total of 1,089,569,365 IU of CINRYZE has been distributed commercially worldwide corresponding to approximately 20,954 patient years. Since post-marketing exposure is based on shipment data, it is not currently possible to break down the patient exposure by region, indication, gender, age, or other factors.

Table SV.1: Cumulative Sales of CINRYZE (10-October-2008 to 30-June-2024)*

	Cumulative
Units distributed	1,089,569,365
Estimated number of patients exposed per month	20,954

*Cumulative average of the estimated number of unique patients exposed during the given period of time.

[redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

CINRYZE has no known potential for abuse or dependence.

[redacted]

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

None.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

None.

Known risks that do not impact the risk-benefit profile:

None.

Other reasons for considering the risks not important:

None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
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 IU/kg) was significantly greater than that recommended for CINRYZE (1,000 IU, equivalent to ~14 IU/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.
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,

[redacted]

Important Identified Risks	Risk-benefit impact
	cancer, cardiac disease, tobacco smoking, high blood 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.
Hypersensitivity reactions	Patients who are treated with human plasma proteins may experience immune responses which could result in hypersensitivity reactions e.g. mild skin rashes or potentially more serious anaphylactic reactions. However, a hypersensitivity reaction is expected to be infrequent as patients who are treated with human plasma proteins may experience immune responses which could result in 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. 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 C1 INH 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.
Adverse events with self or home administration	There is potential for serious adverse events to occur with self or home administration, including but not limited to bleeding, infiltration of subcutaneous tissue leading to localised inflammatory reaction, intra-arterial puncture, air embolisation via indwelling catheters, systemic infusion of heparin used in indwelling catheters, or systemic or localised systemic infection.

Important Potential Risks	Risk-benefit impact
Transmission of infectious disease	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: PEG precipitation, pasteurisation, and nanofiltration to further reduce the possibility of infectious disease

[redacted]

Important Potential Risks	Risk-benefit impact
	transmission.
Medication Error	CINRYZE can be administered at home. Potential risks associated with home-treatment are related to the administration itself. Review of CINRYZE adverse event reports showed that less than 0.2 % of adverse event cases reported serious medication error(s). Inappropriate schedule of product administration due to dose omission or infrequent dosing followed by HAE attack were the most common errors. Inappropriate technique in dose administration was not evident in medication error reports with serious outcome. There was no plausible evidence that overdose of CINRYZE less than 3 times of approved dose was associated with serious outcome.

Missing Information	Risk-benefit impact
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. Data supporting dosing recommendations in children less than 6 years old are very limited. 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	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 embryo-foetal effects of treatment were observed in reproductive studies in rats at dose levels up to 28-times the recommended human dose (1,000 IU) 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.
Limited information is available from the CINRYZE development programme on use in non-Caucasian patients	C1 esterase inhibitor becomes biologically inactive after binding to its target and is then metabolised the same regardless of ethnicity.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

To address the request for supplementary information included in the Type II variation assessment report of procedure EMEA/H/C/001207/II/0104, the missing information "Use in children less than 2 years of age" has been updated to "Use in children less than 6 years of age)".

Across all the clinical studies, there were 61 unique paediatric subjects enrolled and exposed to over 2,500 infusions of CINRYZE (2-5 years, n=3; 6-11 years, n= 32; 12-17 years, n=26). Among these children, the only adverse reactions with CINRYZE included headache, nausea, pyrexia, and infusion site erythema. None of these adverse reactions were severe, and none led to discontinuation of study drug.

Overall, there were no clinically meaningful adverse trends observed in frequency or types of adverse events observed among paediatric subjects compared to adults. No subjects (children) were discontinued from CINRYZE therapy due to an adverse event in any clinical study. Overall, the safety

[redacted]

and tolerability of CINRYZE are similar in children (2-5, 6-11, and 12-17 years old) and adults (≥18 years old).

Considering the limited data available for the children less than 6 years of age, it has been considered as missing information.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Thrombosis with high doses	
Potential mechanisms:	Inhibition of the fibrinolysis system, although not proven. All of the neonates receiving C1 esterase inhibitor (Berinert® P, CSL Behring) at a very high dose (500 U/kg and off-label indication) had congenital heart defects and had undergone extracorporeal circulatory arrest during surgical repair. The marketing authorisation holder (MAH) has shown in vitro testing of healthy human blood samples that CINRYZE, at doses 7 times physiologic, does not promote thrombogenesis. In fact, CINRYZE showed anticoagulant activity.
Evidence source(s) and strength of evidence:	Summary of Clinical Safety.
Characterisation of the risk:	The fatalities reported in the small series of neonates exposed to very high dose of other C1-esterase inhibitor (Berinert®, CSL Behring) for capillary leak is not applicable to current usage of the product. To date, the majority of reported thrombotic events post-marketing for HAE have been associated with a hypercoagulable condition or situation (i.e., indwelling central venous catheter) rather than with very high dose of CINRYZE. Doses of CINRYZE in overdose cases were generally less than 3 times recommended dose. Thus, frequency of thrombosis with high dose cannot be calculated. **Clinical trials**: Cumulatively, 9 cases including 9 events were identified, 8 serious and 1 non-serious. The reported PTs included Cerebrovascular accident (n=2), Deep vein thrombosis (n=2), Acute myocardial infarction (n=1), Arteriovenous fistula thrombosis (n=1), Catheter site thrombosis (n=1), Myocardial infarction (n=1), and Pulmonary embolism (n=1). Outcome of the events were reported as fatal (n=2), not resolved (n=2), resolved with sequelae (n=1) and resolved (n=4). **Post-marketing sources**: Cumulatively, 242 cases with 271 events for thromboembolic events were reported regardless of whether there was CINRYZE overdose; 224 events were serious and 47 events were non-serious. The reported PTs included Thrombosis (n=55), Central venous catheterisation (n=31), Myocardial infarction (n=22), Pulmonary embolism (n=21), Cerebrovascular accident (n=16), Deep vein thrombosis (n=16), Device occlusion (n=16), Thrombosis in device (n=16), Transient ischaemic attack (n=12), Jugular vein thrombosis (n=10), Subclavian vein thrombosis (n=4), Device

Important Identified Risk: Thrombosis with high doses	
	related thrombosis (n=4), Blindness transient (n=3), Embolic stroke (n=3), Pulmonary thrombosis (n=3), Venous thrombosis (n=3), Hemiparesis (n=2), Infusion site thrombosis (n=2), Monoplegia (n=2), Retinal vein thrombosis (n=2), Thrombophlebitis (n=2), and the remaining PTs were reported with a single frequency. Outcome: Fatal (n=10), not resolved (n=21), resolved with sequelae (n=3), resolved (n=76), resolving (n=25), and unknown (n=136). **Background incidence/prevalence** Because CINRYZE is administered to patients with a deficiency (or relative deficiency) in endogenous C1 INH, it is not expected that the prevalence or incidence of thrombotic events would be different than that observed in the general population.
Risk factors and risk groups:	Neonates receiving extremely high doses of a C1 INH product or patients with pre-existing hypercoagulability disorders (i.e. protein C or S deficiency, factor V Leiden, etc.).
Preventability:	Do not administer high doses of CINRYZE to neonates.
Impact on the risk-benefit balance of the product:	The identified risk of thrombosis with high doses can be life threatening but managed effectively within a hospital setting with anticoagulant. Extremely high doses (>500 IU/kg as a single infusion) may be associated with great vessel thrombosis. However, to date, there have been no individual case safety reports (ICSRs) for such high doses. Based on available information, the risk of thrombotic events is more likely related to pre-existing known risk factors, rather than HAE itself or the use of C1 INH. Cases reported during the interval do not alter the benefit-risk profile for product. The MAH will continue to actively monitor this risk.
Public health impact:	Great vessel thrombosis was observed in neonates treated with another plasma-derived C1 esterase inhibitor when used to prevent or treat capillary leak syndrome related to cardiac surgery. This would constitute an off-label use at an extremely high dose (over 500 IU/kg of body weight). The potential public health impact of safety concern is therefore low.

Important Identified Risk: Thrombosis in patients with thrombogenic risk factors	
Potential mechanisms:	Inhibition of the fibrinolysis system although this has not been proven. Nearly all of the ICSRs for thrombotic events in patients receiving CINRYZE were associated with an underlying risk for the event.
Evidence source(s) and strength of evidence:	Summary of Clinical Safety.
Characterisation of the risk:	**Clinical trials**: Cumulatively, 9 cases including 9 events were identified, 8 serious and 1 non-serious. The reported PTs included Cerebrovascular accident (n=2), Deep vein thrombosis (n=2), Acute myocardial infarction (n=1), Arteriovenous fistula thrombosis (n=1), Catheter site thrombosis (n=1), Myocardial infarction (n=1), and Pulmonary

[redacted]

Important Identified Risk: Thrombosis in patients with thrombogenic risk factors	
	embolism (n=1). Outcome of the events were reported as fatal (n=2), not resolved (n=2), resolved with sequelae (n=1) and resolved (n=4). **Post-marketing sources**: Cumulatively, 242 cases with 271 events for thromboembolic events were reported regardless of whether there was CINRYZE overdose; 224 events were serious and 47 events were non-serious. The reported PTs included Thrombosis (n=55), Central venous catheterisation (n=31), Myocardial infarction (n=22), Pulmonary embolism (n=21), Cerebrovascular accident (n=16), Deep vein thrombosis (n=16), Device occlusion (n=16), Thrombosis in device (n=16), Transient ischaemic attack (n=12), Jugular vein thrombosis (n=10), Subclavian vein thrombosis (n=4), Device related thrombosis (n=4), Blindness transient (n=3), Embolic stroke (n=3), Pulmonary thrombosis (n=3), Venous thrombosis (n=3), Hemiparesis (n=2), Infusion site thrombosis (n=2), Monoplegia (n=2), Retinal vein thrombosis (n=2), Thrombophlebitis (n=2), and the remaining PTs were reported with a single frequency. Outcome: Fatal (n=10), not resolved (n=21), resolved with sequelae (n=3), resolved (n=76), resolving (n=25), and unknown (n=136). **Background incidence/prevalence** CINRYZE would be administered to HAE patients who have a deficiency or relative deficiency of C1 INH activity. Patients who receive CINRYZE for long-term prevention of HAE attacks may use indwelling catheters for CINRYZE infusions. It is not known if CINRYZE recipients would have other thrombogenic risk factors at rates different from the general population.
Risk factors and risk groups:	Patients with thrombogenic risk factors including indwelling catheters).
Preventability:	Administer CINRYZE to patients with thrombogenic risk factors only after full consideration of the risk/benefit analysis for the patient.
Impact on the risk-benefit balance of the product:	The identified risk of thrombosis with high doses can be life threatening but managed effectively within a hospital setting with anticoagulant. Routine risk minimisation activities: Labeling The SPC includes the following information which is relevant to minimising the risks of thrombosis in patients with thrombogenic risk factors. 4.4 Special warnings and precautions for use Thrombotic events Thrombotic events have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving off-label high doses of another C1-esterase inhibitor product (up to 500 IU/kg) to prevent capillary leak syndrome. Based upon an animal study there is a potential thrombogenic threshold at doses greater than 200 IU/kg. Patients with known risk factors for thrombotic events (including indwelling catheters) should be

[redacted]

Important Identified Risk: Thrombosis in patients with thrombogenic risk factors	
	monitored closely. The SPC is approved by centralised procedure, thus, there are no differences among regional EEA SPCs. Other routine risk minimisation measures CINRYZE is available as a prescription only medicine.
Public health impact:	Low

Important Identified Risk: Hypersensitivity Reactions	
Potential mechanisms:	Impaired self-tolerance mechanisms or significant genetic variant of endogenous C1 esterase inhibitor
Evidence source(s) and strength of evidence:	Post-marketing data
Characterisation of the risk:	Incidence not known. However, expected to be infrequent as C1 inhibitor [human] is a naturally occurring human plasma protein typically not recognised as "foreign" by a patient's immune system. **Clinical trials**: Cumulatively, 5 cases including 5 events were identified, 4 serious and 1 non-serious. The relevant PTs included Anaphylactic reaction (n=1), Angioedema (n=1), Dyspnoea (n=1), Laryngeal oedema (n=1) and Urticaria (n=1). The outcome of the events was reported as resolved (n=5). **Post-marketing**: Cumulatively 2,864 cases with 3,449 events were reported for this risk, 1,316 serious and 2,133 non-serious events. The relevant PTs included Pharyngeal swelling (n=569), Angioedema (n=551), Swelling (n=550), Laryngeal oedema (n=219), Swelling face (n=218), Rash (n=183), Swollen tongue (n=150), Urticaria (n=127), Dyspnoea (n=116), Pruritus (n=89), Pharyngeal oedema (n=80), Cough (n=77), Lip swelling (n=71), Chest discomfort (n=56), Erythema (n=37), Flushing (n=35), Asthma (n=31), Hypotension (n=30), Rash pruritic (n=24), Eye swelling (n=23), Blood pressure decreased (n=22), and the remaining PTs were reported with frequency less than 20. Outcome: Fatal (n=8), not resolved (n=413), resolved with sequelae (n=4), resolved (n=1,423), resolving (n=166), unknown (n=1,435). **Background incidence/prevalence** Not known.
Risk factors and risk groups:	Autoimmune disease or underlying malignancy.
Preventability:	Known hypersensitivity to the active substance or to any of the excipients is listed as a contraindication in section 4.3 of the SmPC.
Impact on the risk-benefit balance of the product:	As available evidence shows that the incidence of CINRYZE related anaphylactic reaction is low, the benefit-risk of CINRYZE remains positive. Risk minimisation activities might lower

[redacted]

Important Identified Risk: Hypersensitivity Reactions	
	hypersensitivity risk. Routine risk minimisation activities: Labeling. The SPC includes the following information which is relevant to minimising the risks of hypersensitivity reactions: 4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients. 4.4 Special warnings and precautions for use Hypersensitivity As with any biological product hypersensitivity reactions may occur. Hypersensitivity reactions may have symptoms similar to angioedema attacks. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur after administration, they should alert their physician. In case of anaphylactic reactions or shock, emergency medical treatment should be administered. The SPC is approved by centralised procedure, thus, there are no differences among regional EEA SPCs. Other routine risk minimisation measures CINRYZE is available as a prescription only medicine.
Public health impact:	None

Important Identified Risk: Development of C1 INH antibodies	
Potential mechanisms:	Host humoral response to exogenous C1 INH antigen.
Evidence source(s) and strength of evidence:	Summary of clinical safety.
Characterisation of the risk:	**Clinical Trials:** Cumulatively, no cases were reported from clinical trials. **Post-marketing:** Cumulatively 13 cases with 13 events were reported for this risk. Of the 13 events received, 7 events were reported as non-serious and 6 events as serious. The reported PTs included Blood immunoglobulin E increased (n=4), Drug specific antibody present (n=3), Antibody test positive (n=1), Antinuclear antibody positive (n=1), Autoantibody positive (n=1), Blood immunoglobulin M increased (n=1), Drug specific antibody (n=1), and Immunoglobulins increased (n=1). Outcome of the events was reported as not resolved (n=3), resolving (n=1) and unknown (n=9). **Background incidence/prevalence** None.
Risk factors and risk groups:	Unknown
Preventability:	There is no justifiable way to prevent antibody formation, although the risk for HAE patients receiving CINRYZE is low as it is a naturally occurring plasma protein. To date, there have

[redacted]

Important Identified Risk: Development of C1 INH antibodies	
	been some patients and subjects in clinical trials with identified antibody, although the clinical relevance has not been completely characterised. Oftentimes, there is associated autoimmune disease or underlying malignancy.
Impact on the risk-benefit balance of the product:	This is a potential therapeutic class concern that could apply to any exogenously administered human plasma protein. Development of antibody against CINRYZE could reduce efficacy. As the incidence of development of clinically significant levels of anti-CINRYZE antibody is low in Company sponsored interventional clinical studies, the impact of such development on the overall benefit-risk balance is low.
Public health impact:	None ascertained.

Important Identified Risk: Adverse events with self or home administration of CINRYZE	
Potential mechanisms:	Poor administration technique.
Evidence source(s) and strength of evidence:	Summary of Clinical Safety.
Characterisation of the risk:	**Clinical trials**: Cumulatively, no cases were reported from clinical trials. **Post-marketing**: A total of 85 cases with 130 events were received for this risk. Out of 130 events, the events categorized under home administered included 18 cases (28 events), self-administered included 66 cases including 101 events and Infusion site extravasation: 1 case including 1 event. Events categorized under home administration were: Inappropriate schedule of product administration (n=4), Drug ineffective (n=2), and (n=1 each) for Abdominal pain, Adverse event, Catheter site related reaction, Contusion, Device issue, Grip strength decreased, Hereditary angioedema, Hospitalization, Infusion site extravasation, Malaise, Memory impairment, Nasopharyngitis, Nausea, Off-label use, Poor venous access, Pregnancy, Product dose omission issue, Scar, Stress and Swelling. Events categorized under self-administration were Hereditary angioedema (n=15), Poor venous access (n=10), Inappropriate schedule of product administration (n=5), Product administration error (n=4), Incorrect dose administered (n=3), Product dose omission issue (n=3), Vascular access complication (n=3), Wrong technique in product usage process (n=3), Headache (n=2) Influenza (n=2), No adverse event (n=2) and (n=1 each) for Alopecia, Anxiety, Arthropathy, Arthropod bite, Asthma, Balance disorder, Chapped lips, Conjunctival hyperaemia, COVID-19, Depression, Drug ineffective, Feeling abnormal, Frustration tolerance decreased, Gastrointestinal infection, Head injury, Hepatic enzyme increased, Herpes zoster, Illness, Incorrect drug administration rate, Incorrect route of product administration, Infection, Infusion site bruising, Intentional self-injury, Laryngeal edema, Loss of consciousness, Nausea, Necrosis, Neoplasm malignant, Nervousness, Off-label use, Pharyngeal edema, Poor quality

Important Identified Risk: Adverse events with self or home administration of CINRYZE	
	product administered, Product prescribing error, Product storage error, Rash, Renal function test abnormal, Repetitive speech, Restless legs syndrome, Sepsis, Stress, Suicidal ideation, Swelling, Swelling face, Therapy change, Tongue, oedema, Tracheal disorder, Unevaluable event, Weight decreased and Weight increased. Seriousness/Outcome: There is potential for serious adverse events to occur with self or home administration, including but not limited to bleeding, infiltration of subcutaneous tissue leading to localized inflammatory reaction, intra-arterial puncture, air embolisation via indwelling catheters, systemic infusion of heparin used in indwelling catheters, or systemic or localized systemic infection. **Background incidence/prevalence** Not Applicable.
Risk factors and risk groups:	Patients receiving CINRYZE by self or home administration.
Preventability:	Institution of self or home administration training by qualified healthcare professionals (HCPs) will greatly decrease the risk for AEs related to self-administration. Patient and caregiver demonstration of specific knowledge of the HAE disease process and proper administration technique to their health care provider prior to instituting such home based therapy would be instrumental to the training process. As a condition of approval in the EU under the centralised procedure, each country must review and approve the self-administration training materials before CINRYZE could be launched in that particular Member State.
Impact on the risk-benefit balance of the product:	Routine risk minimisation activities: Labeling. The SmPC includes the following information which is relevant to minimising the risks of adverse events with self- or home administration: 4.4 Special warnings and precautions for use: Home-treatment and self-administration There are limited data on the use of this medicinal product in home- or self-administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of adverse drug reactions (ADR), particularly hypersensitivity. The decision on the use of home-treatment for an individual patient should be made by the treating physician, who should ensure that appropriate training is provided, and the use reviewed at intervals. 6.6 Special precautions for disposal and other handling Reconstitution and administration of CINRYZE: Reconstitution, product administration and handling of the administration set, and needles must be done with caution. Use either the filter transfer device provided with CINRYZE or a commercially available double-ended needle. Preparation and handling: CINRYZE is intended for intravenous administration after reconstitution with water for injections. CINRYZE vial is for single-use only.

[redacted]

Important Identified Risk: Adverse events with self or home administration of CINRYZE	
	Reconstitution: One powder vial, 1 solvent vial, 1 filter transfer device, 1 disposable 10 mL syringe, 1 venipuncture set and 1 protective mat is needed to prepare one dose of 500 IU. Two powder vials, 2 solvent vials, 2 filter transfer devices, 1 disposable 10 mL syringe, 1 venipuncture set and 1 protective mat is needed to prepare one dose of 1,000 IU. Each product vial should be reconstituted with 5 mL water for injections. One vial of reconstituted CINRYZE corresponds to a dose of 500 IU. Two vials of reconstituted CINRYZE correspond to a dose of 1,000 IU. Therefore, two vials are combined for one dose of 1,000 IU. 1. Work on the mat provided and wash your hands before performing the following procedures. 2. Aseptic technique should be used during the reconstitution procedure. 3. Ensure the powder vial and the solvent vial are at room temperature (15ºC - 25ºC). 4. Release the powder vial label by peeling down the purple strip indicated by the arrow. 5. Remove plastic caps from the powder and solvent vials. 6. Cleanse stoppers with a disinfection swab and allow them to dry prior to use. 7. Remove protective covering from the top of the transfer device package. Do not remove the device from the package. 8. Note: the transfer device must be attached to the solvent vial before being attached to the powder vial, so that the vacuum in the powder vial is not lost. Place the solvent vial on a flat surface and insert the blue end of the transfer device into the solvent vial, pushing down until the spike penetrates through the center of the solvent vial stopper and the device snaps in place. The transfer device must be vertical prior to penetrating the stopper closure. 9. Remove the plastic package from the transfer device and discard it. Take care not to touch the exposed end of the transfer device. 10. Place the powder vial on a flat surface. Invert the transfer device and the solvent vial containing water for injections and insert the clear end of the transfer device into the powder vial, pushing down until the spike penetrates the rubber stopper and the transfer device snaps into place. The transfer device must be vertical prior to penetrating the stopper closure of the powder vial. The vacuum in the powder vial will draw in the solvent. If there is no vacuum in the vial, do not use the product. 11. Gently swirl the powder vial until all powder is dissolved. Do not shake the powder vial. Make sure all the powder is completely dissolved. 12. Disconnect the solvent vial by turning it anti-clockwise. Do

[redacted]

Important Identified Risk: Adverse events with self or home administration of CINRYZE	
	not remove the clear end of the transfer device from the powder vial. One vial of reconstituted CINRYZE contains 500 IU of human C1-esterase inhibitor in 5 ml, resulting in a concentration of 100 IU/mL. Proceed to administration process if patients receive a dose of 500 IU. Two vials of CINRYZE powder must be reconstituted to make one dose (1,000 IU/10 mL). Therefore, repeat instructions 1 to 12 above using an additional package containing a transfer device to reconstitute the second of two powder vials. Do not reuse the transfer device. Once the two vials are reconstituted proceed to administration process for a dose of 1,000 IU. <u>Administration process for a dose of 500 IU</u> 1. Aseptic technique should be used during the administration procedure. 2. After reconstitution, the CINRYZE solutions are colourless to slightly blue and clear. Do not use the product if the solutions are turbid or discoloured. 3. Using a sterile, disposable 10 mL syringe, draw back the plunger to allow approximately 5 mL of air into the syringe. 4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise. 5. Invert the vial gently and inject air into the solution and then slowly withdraw the reconstituted CINRYZE solution into the syringe. 6. Detach the syringe from the vial by turning it anti-clockwise and releasing it from the clear end of the transfer device. 7. Inspect the reconstituted CINRYZE solution for particulate matter prior to administration; do not use if particles are observed. 8. Attach the venipuncture set to the syringe containing CINRYZE solution and inject intravenously into the patient. Administer 500 IU (reconstituted in 5 ml of water for injections) of CINRYZE by intravenous injection at a rate of 1 ml per minute over 5 minutes. <u>Administration process for a dose of 1,000 IU</u> 1. Aseptic technique should be used during the administration procedure. 2. After reconstitution, the CINRYZE solutions are colourless to slightly blue and clear. Do not use the product if the solutions are turbid or discoloured. 3. Using a sterile, disposable 10 mL syringe, draw back the plunger to allow approximately 5 mL of air into the syringe. 4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise. 5. Invert the vial gently and inject air into the solution and then slowly withdraw the reconstituted CINRYZE solution into the syringe. 6. Detach the syringe from the vial by turning it anti-

Important Identified Risk: Adverse events with self or home administration of CINRYZE	
	clockwise and releasing it from the clear end of the transfer device. 7. Using the same syringe, repeat steps 3 to 6 with a second vial of reconstituted CINRYZE to make one complete 10 mL dose. 8. Inspect the reconstituted CINRYZE solution for particulate matter prior to administration; do not use if particles are observed. 9. Attach the venipuncture set to the syringe containing CINRYZE solution and inject intravenously into the patient. Administer 1,000 IU (reconstituted in 10 mL of water for injections) of CINRYZE by intravenous injection at a rate of 1 mL per minute over 10 minutes. Any unused product or waste material should be disposed of in accordance with local requirements. The SPC is approved by centralised procedure, thus, there are no differences among regional EEA SPCs. Other routine risk minimisation measures CINRYZE is available as a prescription only medicine. Additional risk minimisation measures: • Educational material for healthcare professionals. • Educational materials for non-healthcare professionals.
Public health impact:	None ascertained.

Important Potential Risk: Transmission of infectious disease	
Potential mechanisms:	Direct transmission.
Evidence source(s) and strength of evidence:	Summary of Clinical Safety.
Characterisation of the risk:	**Clinical trials**: Cumulatively, no cases were reported from clinical trials. **Post-marketing**: Cumulatively, 4 cases with 4 events were reported for this risk. The reported PTs included Hepatitis C (n=3) and HIV test positive (n=1). All the events were serious. Outcome: Not resolved (n=4). **Background incidence/prevalence** • Approximately, one blood transfusion in 205,000 transmits an HBV infection, and one blood transfusion in about 2 million transmits HCV. The risk of HIV transmission from a transfusion is about one in 2,135,000. • Diseases caused by certain bacteria, viruses, and parasites, such as babesiosis, Chagas disease, malaria, Lyme disease, and others can also be spread by blood product transfusions.
Risk factors and risk groups:	Inadequate manufacturing techniques. Unsanitary equipment. Failed screening of plasma donors.
Preventability:	CINRYZE is manufactured using a heating step, PEG

[redacted]

Important Potential Risk: Transmission of infectious disease	
	precipitation and a 15 nm nanofiltration step which effectively removes all enveloped and non-enveloped viruses. In addition, experimental evidence confirms that this latter nanofiltration step completely removes the 236K prion protein associated with sheep scrapie. The product will be administered with sterile equipment appropriate for IV administration.
Impact on the risk-benefit balance of the product:	As with all agents derived from human sources there is a theoretical risk of transmission of infectious disease which can potentially be life threatening or fatal. There is no confirmed transmission of infectious agents due to contaminated CINRYZE product. Transmission risks remain potential. Routine risk minimisation activities: Labeling The SPC includes the following information which is relevant to minimising the risks of transmission of infectious diseases: 4.4 Special warnings and precautions for use Traceability In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Transmissible agents Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped viruses HAV and parvovirus B19. Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived C1 inhibitor product. The SmPC is approved by centralised procedure, thus, there are no differences among regional EEA SPCs. Other routine risk minimisation measures CINRYZE is available as a prescription only medicine.
Public health impact:	For transmission of infection with CINRYZE (or other C1 INH to our knowledge), the public health concern is minimal.

Important Potential Risk: Medication Error	
Potential mechanisms:	Not applicable.
Evidence source(s) and strength of evidence:	Gower et al, 2011 [redacted]
Characterisation of the risk:	**Clinical trials**: Cumulatively 9 cases with 9 events were reported for this risk. All the events were reported as non-serious. The relevant PTs

[redacted]

Important Potential Risk: Medication Error	
	included Medication error (n=5), Product storage error (n=2), Inappropriate schedule of product administration (n=1), and Product administration error (n=1). The outcome of the events was reported as resolved (n=7), not resolved (n=1) and unknown (n=1). **Post-marketing**: Cumulatively, 7,613 cases with 9,247 events were reported for this risk, 31 serious and 9,216 non-serious. The relevant PTs included Inappropriate schedule of product administration (n=3,397), Prescribed overdose (n=2,958), Product use in unapproved indication (n=1,169), Product dose omission issue (n=892), Product use issue (n=244), Incorrect dose administered (n=96), Incorrect product administration duration (n=81), Wrong technique in product usage process (n=57), Incorrect route of product administration (n=46), Extra dose administered (n=45), Overdose (n=43), Incorrect drug administration rate (n=41), Underdose (n=33), Prescribed underdose (n=26), Product administration error (n=24), Product storage error (n=20), Product preparation issue (n=13), Product prescribing error (n=11), Product administered to patient of inappropriate age (n=11), and the remaining PTs were reported with frequency less than 10. Outcome: Fatal (n=5), not resolved (n=4,099), resolved with sequelae (n=1), resolved (n=1,282), resolving (n=25), and Unknown (3,835). **Background incidence/prevalence** Not measurable.
Risk factors and risk groups:	Patients with poorly controlled HAE may require higher than labeled doses, whereas patients with well controlled HAE may be prescribed a lesser frequency of dosing by their health care provider.
Preventability:	As discussed, health care providers may alter the frequency or number of doses of CINRYZE based on the patient's response to therapy. The current package insert adequately describes the risks associated with CINRYZE use.
Impact on the risk-benefit balance of the product:	To date, there has been no safety signal associated with medication error reports that significantly impact the benefit-risk balance. Routine risk minimisation activities: Labeling The SPC includes the following information which is relevant to minimising the risks of medication errors. 4. CLINICAL PARTICULARS 4.2 Posology and method of administration CINRYZE therapy should be initiated under supervision of a physician experienced in the care of patients with HAE. Posology Adults *Treatment of angioedema attacks:* • 1,000 IU of CINRYZE at the first sign of the onset of an

Important Potential Risk: Medication Error

angioedema attack.

- A second dose of 1,000 IU may be administered if the patient has not responded adequately after 60 minutes.
- For patients experiencing laryngeal attacks or if initiation of treatment is delayed, the second dose can be given sooner than 60 minutes.

Routine prevention of angioedema attacks:

1,000 IU of CINRYZE every 3 or 4 days is the recommended starting dose for routine prevention against angioedema attacks; the dosing interval may need to be adjusted according to individual response. The continued need for regular prophylaxis with CINRYZE should be reviewed on a regular basis.

Pre-procedure prevention of angioedema attacks:

1,000 IU of CINRYZE within 24 hours before a medical, dental, or surgical procedure.

Paediatric population

Adolescents: For treatment, routine prevention, and pre-procedure prevention in adolescents 12 to 17 years old, the dose is the same as for adults.

Children: The safety and efficacy of CINRYZE in children less than 2 years old has not been established. Data supporting dosing recommendations in children less than 6 years old are very limited. Currently available data are described in sections 4.8, 5.1 and 5.2.

The SmPC contains the following information:

Treatment of angioedema attacks	Pre-procedure prevention of angioedema attacks	Routine prevention of angioedema attacks
2 to 11 years, >25 kg: 1,000 IU of CINRYZE at the first sign of the onset of an acute attack. A second dose of 1,000 IU may be administered if the patient has not responded adequately after 60 minutes.	*2 to 11 years, >25 kg:* 1,000 IU of CINRYZE within 24 hours before a medical, dental, or surgical procedure.	*6 to 11 years:* 500 IU of CINRYZE every 3 or 4 days is the recommended starting dose for routine prevention against angioedema attacks. The dosing interval and dose may need to be adjusted according to individual response. The continued need for regular prophylaxis with CINRYZE should be reviewed on a
2 to 11 years, 10-25 kg: 500 IU of CINRYZE at the first sign of the onset of an acute attack. A second dose of 500 IU may be	*2 to 11 years, 10-25 kg:* 500 IU of CINRYZE within 24 hours before a medical, dental, or surgical	

[redacted]

Important Potential Risk: Medication Error	
	administered if the patient has not responded adequately after 60 minutes. | procedure. | regular basis. Elderly patients: No special investigations have been performed. For treatment, routine prevention and pre-procedure prevention in elderly patients, 65 years of age or older, the dose is the same as for adults. Patients with renal or hepatic impairment: No special investigations have been performed. For treatment, routine prevention and pre-procedure prevention in patients with renal or hepatic impairment, the dose is the same as for adults. Method of administration: Intravenous use. The reconstituted product should be administered by intravenous injection at a rate of 1 mL per minute. For instructions on reconstitution of the medicinal product before administration, see section 6.6. 4.4 Special warnings and precautions for use Thrombotic events: Thrombotic events have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving off-label high doses of another C1-esterase inhibitor product (up to 500 IU/kg) to prevent capillary leak syndrome. Based upon an animal study there is a potential thrombogenic threshold at doses greater than 200 IU/kg. Patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely. Paediatric population: Thrombotic events have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving off-label high doses of another C1-esterase inhibitor product (up to 500 IU/kg) to prevent capillary leak syndrome. The SPC is approved by centralised procedure, thus, there are no differences among regional EEA SPCs. Other routine risk minimisation measures CINRYZE is available as a prescription only medicine.
Public health impact:	None

SVII.3.2. Presentation of the missing information

Missing information: Use in children less than 6 years	
Evidence source:	The safety and efficacy of CINRYZE in children less than 6 years old has not been established. Data supporting dosing recommendations in children less than 6 years old are very limited. 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.

[redacted]

Missing information: Limited information is available for use in pregnancy	
Evidence source:	Pregnancy Human C1-esterase inhibitor is a physiological component of human plasma. Therefore, no adverse effects on fertility, pre- and post-natal development are expected in humans. Animal-reproductive studies show no maternal or embryo-foetal effects in rats at dose levels up to 28 times the recommended human dose (1,000 IU) based on an average adult body weight of 70 kg. Data on a limited number of exposed pregnancies are available from clinical studies and from post-marketing experience (including data from two observational studies) and indicate no adverse effects of Human C1-esterase inhibitor on pregnancy or on the health of the foetus/newborn child. 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 post-natal development, or carcinogenicity studies were conducted.

Missing information: Limited information is available from the CINRYZE development programme on use in non-Caucasian patients	
Evidence source:	C1 esterase inhibitor becomes biologically inactive after binding to its target and is then metabolised the same regardless of ethnicity.

[redacted]

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of Safety Concerns	
Important identified risks	• Thrombosis with high doses. • Thrombosis in patients with thrombogenic risk factors. • Hypersensitivity reactions. • Development of C1INH antibodies. • Adverse events with self or home administration.
Important potential risks	• Transmission of infectious diseases. • Medication error.
Missing information	• Use in children less than 6 years of age. • Limited information is available for use in pregnancy. • Limited information is available from the CINRYZE development programme on use in non-Caucasian patients.

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

Specific adverse reaction follow-up questionnaires for:

None.

Other forms of routine pharmacovigilance activities:

None.

III.2. Additional pharmacovigilance activities

None.

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Requesting/Concerned Health Authority	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation					
Not applicable					
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances					
Not applicable					
Category 3 - Required additional pharmacovigilance activities					
Not applicable					

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are conditions of the marketing authorisation				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

[redacted]

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risk: Thrombosis with high doses	**Routine risk communication:** SmPC section 4.4 'Special warnings and Precautions', under 'Thrombotic events'. Venous thrombosis is listed as an uncommon ADR in the SmPC section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Patients with known risk factors for thrombotic events should be monitored closely is recommended in section 4.4 of SmPC. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Important Identified Risk: Thrombosis in patients with thrombogenic risk factors	**Routine risk communication:** SmPC section 4.4 'Special warnings and Precautions', under 'Thrombotic events'. Venous thrombosis is listed as an uncommon ADR in the SmPC section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Patients with known risk factors for thrombotic events should be monitored closely is recommended in section 4.4 of SmPC. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Important Identified Risk: Hypersensitivity reactions	**Routine risk communication:** SmPC section 4.3 under 'Contraindications'. SmPC section 4.4 'Special warnings and Precautions', under 'Hypersensitivity'. Hypersensitivity is listed as common ADR in the SmPC section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Patients should be informed of the early signs of hypersensitivity reactions including hives, urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis is recommended in section 4.4 of SmPC. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Important Identified Risk: Development of C1 INH antibodies	**Routine risk communication:** None proposed. **Routine risk minimisation activities recommending specific clinical**

Safety concern	Routine risk minimisation activities
	measures to address the risk: None proposed. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Important Identified Risk: Adverse events with self or home administration	**Routine risk communication:** SmPC section 4.4 'Special warnings and Precautions', under 'Home-treatment and self-administration'. SmPC section 6.6 'Special precautions for disposal and other handling'. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Physicians to ensure that appropriate training is provided before patient does home-treatment as recommended by section 4.4 of SmPC. Reconstitution, product administration and handling of the administration set and needles must be done with caution as recommended in section 6.6 of SmPC. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Important Potential Risk: Transmission of infectious diseases	**Routine risk communication:** SmPC section 4.4 'Special warnings and Precautions', under 'Transmissible agents'. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Important Potential Risk: Medication error	**Routine risk communication:** SmPC section 4.2 'Posology and method of administration'. SmPC section 4.4 'Special warnings and precautions for use' under 'Paediatric population'. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Thrombotic events have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving off-label high doses of another C1-esterase inhibitor product (up to 500 IU/kg) to prevent capillary leak syndrome. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Missing Information: Use in children less than 6 years of age	**Routine risk communication:** SmPC section 4.2 'Posology and method of administration'. SmPC section 4.4 'Special warnings and precautions for use' under 'Paediatric population'. SmPC section 4.8 'Undesirable effects' under 'Paediatric population'.

[redacted]

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Missing Information: Limited information is available for use in pregnancy	**Routine risk communication:** SmPC section 4.6 'Fertility, pregnancy and lactation'. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** CINRYZE should be given to pregnant women only if clearly indicated. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.
Missing Information: Limited information is available from the CINRYZE development programme on use in non-Caucasian patients	**Routine risk communication:** SPC section 5.2 'Pharmacokinetic properties'. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

Educational material for Healthcare Professionals (HCP) in Europe

Objectives:

These materials are to help HCP to provide training and education to patients/caregivers who are eligible to administer CINRYZE at home, and to ensure that CINRYZE is used appropriately. It is the responsibility of the prescribing doctor to ensure that these patients or their caregivers have all the necessary skills and training to administer CINRYZE appropriately and to regularly check these skills are maintained.

Rationale for the additional risk minimisation activity:

There are limited data on the use of this medicinal product in home- or self-administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of ADRs, particularly hypersensitivity.

Target audience and planned distribution path:

Distributed to prescribers, by sales and/or medical field personnel or posted online and depending on local implementation plan within a country.

Educational material for Patients and Caregivers

Objectives:

Provides a resource for patients/caregivers on how to prepare and administer CINRYZE.

Rationale for the additional risk minimisation activity:

There are limited data on the use of this medicinal product in home- or self-administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of ADRs, particularly hypersensitivity.

[redacted]

Target audience and planned distribution path:

Distributed to patients/caregivers by the prescriber.

Patient Diary

Objectives:

Allows patients/caregivers to record details of each dose of CINRYZE they administer. Patients should bring the diary to each follow-up appointment.

Rationale for the additional risk minimisation activity:

There are limited data on the use of this medicinal product in home- or self-administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of ADRs, particularly hypersensitivity.

Target audience and planned distribution path:

Distributed to prescribers, typically by sales and/or medical field personnel and depending on local implementation plan within a country. Provided to patient by the prescriber.

The information provided in the diary would enable prescribers in evaluating the effectiveness and adverse reactions associated with home administration by their patients.

Judging from the fact that post-marketing reporting of serious medication errors is very rare, the risk minimisation program appears to be effective.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk: Thrombosis with high doses	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Thrombotic events'. SmPC section 4.8. **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important Identified Risk: Thrombosis in patients with thrombogenic risk factors	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Thrombotic events'. SmPC section 4.8. **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important Identified Risk: Hypersensitivity reactions	**Routine risk minimisation measures:** SmPC section 4.3 under 'Contraindications'. SmPC section 4.4 'Special warnings and Precautions', under 'Hypersensitivity'.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.8. **Additional risk minimisation measures:** No risk minimisation measures.	
Important Identified Risk: Development of C1 INH antibodies	**Routine risk minimisation measures:** None Proposed. **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important Identified Risk: Adverse events with self or home administration	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Home-treatment and self-administration'. SmPC section 6.6 'Special precautions for disposal and other handling'. Prescription only medicine. **Additional risk minimisation measures:** Educational material for Healthcare Professionals and non-Healthcare Professionals.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important Potential Risk: Transmission of infectious diseases	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Transmissible agents'. **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important Potential Risk: Medication error	**Routine risk minimisation measures:** SmPC section 4.2 'Posology and method of administration'. SmPC section 4.4 'Special warnings and precautions for use' under 'Paediatric population'. **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing Information: Use in children less than 6 years of age	**Routine risk minimisation measures:** SmPC section 4.2 'Posology and method of administration'. SmPC section 4.4 'Special warnings and precautions for use' under	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	'Paediatric population'. SmPC section 4.8 'Undesirable effects' under 'Paediatric population'. **Additional risk minimisation measures:** No risk minimisation measures.	**Additional pharmacovigilance activities:** None.
Missing Information: Limited information is available for use in pregnancy	**Routine risk minimisation measures:** SmPC section 4.6 'Fertility, pregnancy and lactation'. **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing Information: Limited information is available from the CINRYZE development programme on use in non-Caucasian patients	**Routine risk minimisation measures:** None Proposed. **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for CINRYZE (Human C1 Esterase inhibitor)

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

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

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

I. The medicine and what it is used for

CINRYZE is authorised for:

- Treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE).
- Routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.

Kindly refer to the SmPC for the full indication. CINRYZE contains Human C1-esterase inhibitor as the active substance, and the reconstituted product should be administered by intravenous injection at a rate of 1 mL per minute.

Further information about the evaluation of CINRYZE’s benefits can be found in CINRYZE’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/CINRYZE.

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

Important risks of CINRYZE, together with measures to minimise such risks and the proposed studies for learning more about CINRYZE '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, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of CINRYZE, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

[redacted]

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including periodic safety update report 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 CINRYZE is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of CINRYZE 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 CINRYZE. 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);

Summary of Safety Concerns	
Important identified risks	• Thrombosis with high doses • Thrombosis in patients with thrombogenic risk factors • Hypersensitivity reactions • Development of C1INH antibodies • Adverse events with self or home administration
Important potential risks	• Transmission of infectious diseases • Medication error
Missing information	• Use in children less than 6 years of age • Limited information is available for use in pregnancy • Limited information is available from the CINRYZE development programme on use in non-Caucasian patients

II.B Summary of important risks

Important Identified Risk: Thrombosis with high doses	
Evidence for linking the risk to the medicine	Summary of clinical safety.
Risk factors and risk groups	Neonates receiving extremely high doses of a C1 INH product or patients with pre-existing hypercoagulability disorders (i.e., protein C or S deficiency, factor V Leiden, etc.).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Thrombotic events'. SmPC section 4.8. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Important Identified Risk: Thrombosis in patients with thrombogenic risk factors	
Evidence for linking the risk to the medicine	Summary of clinical safety.
Risk factors and risk groups	Patients with thrombogenic risk factors including indwelling catheters.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Thrombotic events'. SmPC section 4.8. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Important Identified Risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Post-marketing data.
Risk factors and risk groups	Autoimmune disease or underlying malignancy.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3 under 'Contraindications'. SmPC section 4.4 'Special warnings and Precautions', under 'Hypersensitivity'. SmPC section 4.8. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Important Identified Risk: Development of C1 INH antibodies	
Evidence for linking the risk to the medicine	Summary of clinical safety.
Risk factors and risk groups	Unknown.
Risk minimisation measures	**Routine risk minimisation measures:** None. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Important Identified Risk: Adverse events with self or home administration	
Evidence for linking the risk to the medicine	Summary of clinical safety.
Risk factors and risk groups	Patients receiving CINRYZE by self or home administration.

[redacted]

Important Identified Risk: Adverse events with self or home administration	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Home-treatment and self-administration'. SmPC section 6.6 'Special precautions for disposal and other handling'. Prescription only medicine. **Additional risk minimisation measures:** Educational material for Healthcare Professionals and non-Healthcare Professionals.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Important Potential Risk: Transmission of infectious diseases	
Evidence for linking the risk to the medicine	Summary of clinical safety.
Risk factors and risk groups	Inadequate manufacturing techniques. Unsanitary equipment. Failed screening of plasma donors.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 'Special warnings and Precautions', under 'Transmissible agents'. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Important Potential Risk: Medication error	
Evidence for linking the risk to the medicine	Literature.
Risk factors and risk groups	Patients with poorly controlled HAE may require higher than labeled doses, whereas patients with well controlled HAE may be prescribed a lesser frequency of dosing by their health care provider.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 'Posology and method of administration'. SmPC Section 4.4 'Special warnings and precautions for use' under 'Paediatric population'. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Missing Information: Use in children less than 6 years of age	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 'Posology and method of administration'.

[redacted]

Missing Information: Use in children less than 6 years of age	
	SmPC section 4.4 'Special warnings and precautions for use' under 'Paediatric population'. SmPC section 4.8 'Undesirable effects' under 'Paediatric population'. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Missing Information: Limited information is available for use in pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 'Fertility, pregnancy and lactation'. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Missing Information: Limited information is available from the CINRYZE development programme on use in non-Caucasian patients	
Risk minimisation measures	**Routine risk minimisation measures:** None. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

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 CINRYZE.

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

There are no studies required for CINRYZE.

[redacted]

Part VII: Annexes

[redacted]

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

[redacted]

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

[redacted]

[redacted]

[redacted]

Annex 6: Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

Prior to the approval of educational materials in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at materials are to help HCP to provide training and education to patients/caregivers who are eligible to administer CINRYZE at home, and to ensure that CINRYZE is used appropriately, a resource for patients/caregivers on how to prepare and administer CINRYZE and patient dairy allows patients/caregivers to record details of each dose of CINRYZE they administer.

The MAH shall ensure that in each Member State where CINRYZE is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe or use CINRYZE have access are provided with the following educational package:

- Physician educational material.
- Patients and caregivers guide.
- Patient dairy.

Physician educational material:

- Guide for healthcare professionals.
- Healthcare professionals training material.

Guide for healthcare professionals:

- Dosing recommendations for children, adolescents and adults.
- Instructions for preparation, handling and administration of CINRYZE.
- Instructions to provide training on preparation, handling and administration of CINRYZE at home to non-HCPs and patients.

Healthcare professionals training material:

- Information on the approved indication according to the SmPC.
- Detailed description of the administration procedures of CINRYZE.
- Patient's preparation for the procedure and subsequent monitoring.

The patient information pack:

- Patient information leaflet.
- A patient/carer guide.
- A patient diary.

Patient/carer guide:

Note: The suggested key elements below are not supposed to be strictly used only for the related specific tool.

- Detailed description of the modalities used for the self-administration of CINRYZE.
- Recommendations for the planning of the monitoring schedule.

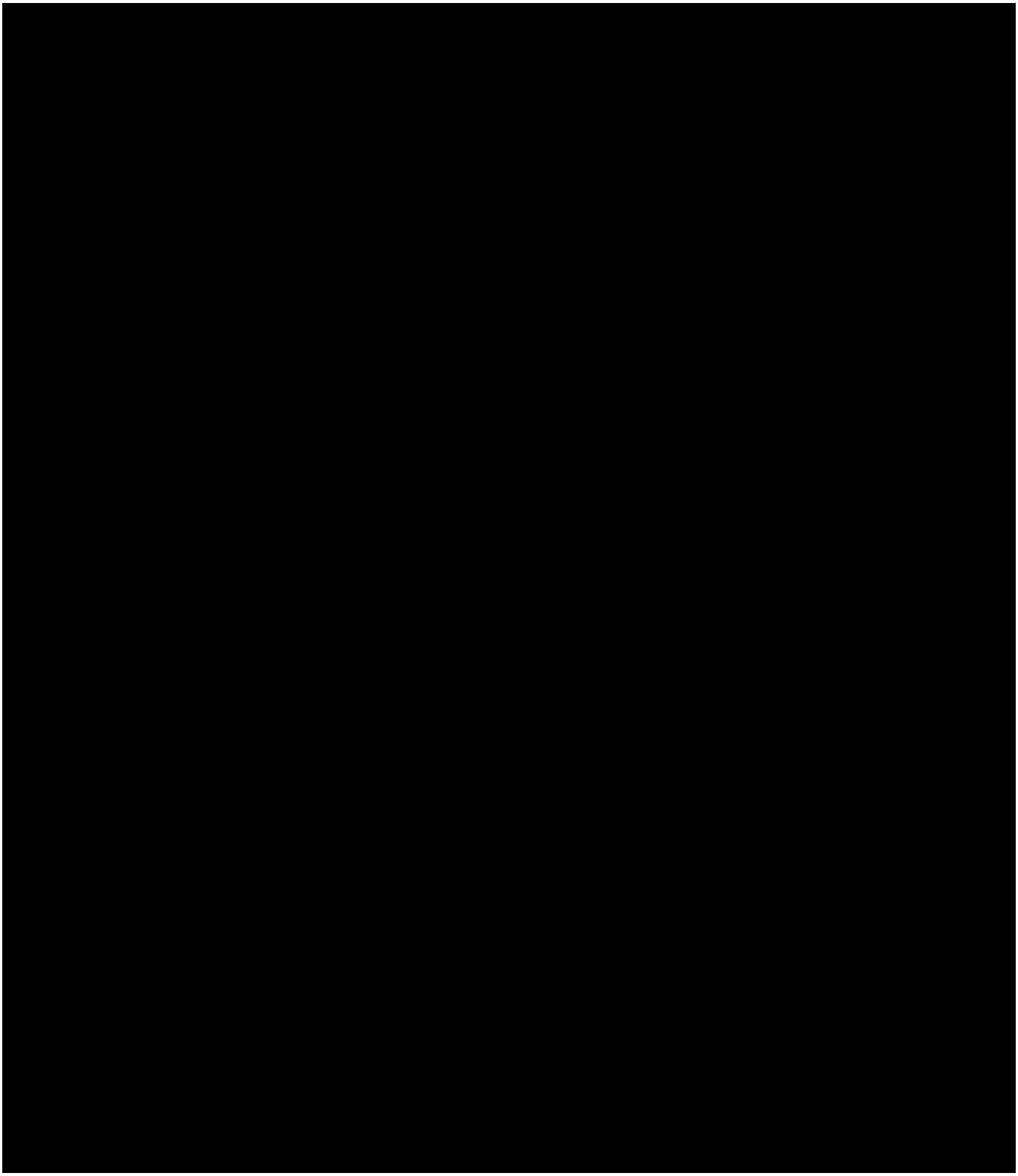
Patient diary:

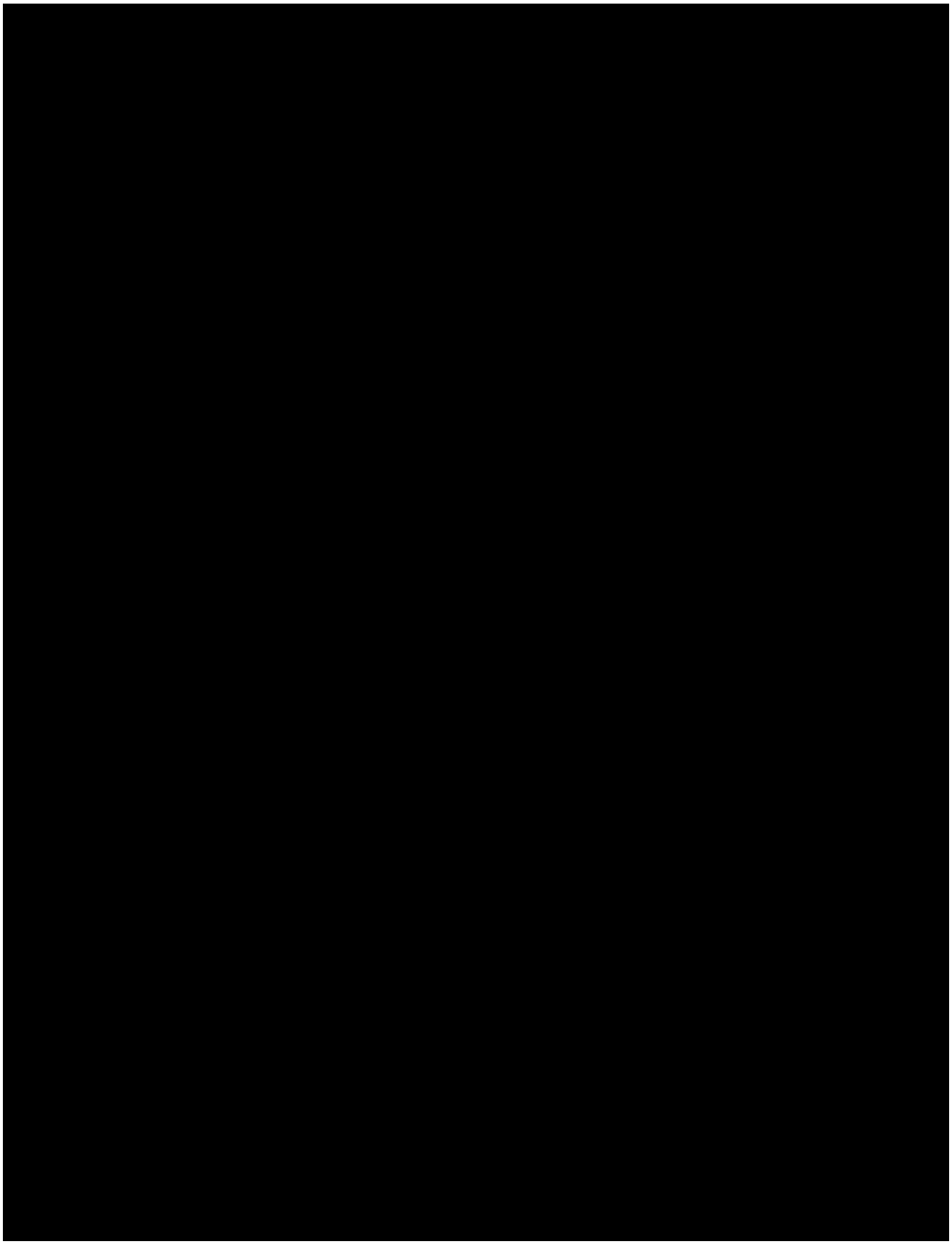
- A graphical guide to using CINRYZE.
- Questionnaires to help patients remember the key steps in preparing and using CINRYZE.

[redacted]

- Reporting of adverse events.

[redacted]





[redacted]