ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cinryze 500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE 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/ml. 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White powder.
The solvent is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Cinryze therapy should be initiated under supervision of a physician experienced in the care of patients with hereditary angioedema (HAE).

Posology

Adults

Treatment of angioedema attacks
- 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.

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.

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, 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, > 25 kg:* 1 000 IU of Cinryze within 24 hours before a medical, dental, or surgical procedure. *2 to 11 years, 10 – 25 kg:* 500 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 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

For intravenous use only.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

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 Units(*****)/kg) to prevent capillary leak syndrome. Based upon an animal study there is a potential thrombogenic threshold at doses greater than 200 Units(*****)/kg. Patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely.

(*****) *[Historically assigned potency values were relative to an in-house reference standard whereby 1 Unit (U) is equal to the mean quantity of C1-esterase inhibitor present in 1 ml of normal human plasma.] An international reference standard (IU) has now been implemented where IU is also defined as the amount of C1-esterase inhibitor present in 1 ml of normal human plasma.*

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-esterase inhibitor product.

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, generalised 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.

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 reactions, 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.

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 Units(*)/kg) to prevent capillary leak syndrome.

Sodium

This medicinal product contains 11.5 mg sodium per vial, equivalent to 0.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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 embryofoetal 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 (see section 5.1).

Cinryze should be given to pregnant women only if clearly indicated.

Breast-feeding

It is unknown whether human C1-esterase inhibitor is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Cinryze therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No specific studies on fertility, early embryonic and postnatal development, or carcinogenicity studies were conducted (see section 5.3).

4.7 Effects on ability to drive and use machines

Based upon the clinical data currently available, Cinryze has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The very common adverse reactions observed following Cinryze infusion in clinical studies were headache and nausea.

Tabulated list of adverse reactions

Adverse reaction frequencies were estimated from 2 pivotal placebo-controlled and 2 open-label studies in 251 unique subjects. Only frequencies based on reporting rates from clinical trials are used to assign frequency category.

Adverse reactions to treatment with Cinryze are classified by MedDRA System Organ Class and absolute frequency in Table 1. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data).

Table 1 Adverse reactions reported in clinical studies and in post marketing reports

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Common	Hypersensitivity
Metabolism and nutrition disorders	Uncommon	Hyperglycaemia
Nervous system disorders	Very common	Headache
	Common	Dizziness
Vascular disorders	Uncommon	Venous thrombosis, phlebitis, venous burning, hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting
	Uncommon	Diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Common	Rash, erythema, pruritus
	Uncommon	Contact dermatitis
Musculoskeletal and connective tissue disorders	Uncommon	Joint swelling, arthralgia, myalgia
General disorders and administration site conditions	Common	Injection site rash/erythema, infusion site pain, pyrexia
	Uncommon	Chest discomfort

Description of selected adverse reactions

Among reports of venous thrombosis, the most common underlying risk factor was presence of an indwelling catheter.

Local reactions at the injection site were uncommon. In clinical studies local reactions (described as pain, bruising, or rash at the injection/catheter site, venous burning or phlebitis) occurred in association with approximately 0.2 % of infusions.

Paediatric population

Across 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 medicinal product.

Overall, the safety and tolerability of Cinryze are similar in children, adolescents and adults. For safety with respect to transmissible agents, see section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in hereditary angioedema, C1-esterase inhibitor, plasma derived, ATC code: B06AC01.

Mechanism of action

C1-esterase inhibitor is a member of the serine protease inhibitor, or serpin, superfamily of proteins. The main function of serpins is to regulate the activity of serine proteases. C1-esterase inhibitor is a single chain glycoprotein found in plasma which, in its mature state, consists of 478 amino acids with an apparent molecular weight of 105 kD.

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 swelling.

Pharmacodynamic effects

In clinical studies, the intravenous administration of Cinryze resulted in a significant increase in systemic levels of antigenic and functional C1-esterase inhibitor within 1 hour after administration. Administration of C1-esterase inhibitor increases serum levels of C1-esterase inhibitor activity and

temporarily restores the natural regulation of the contact, complement, and fibrinolytic systems thereby controlling the swelling or the propensity to swell.

Low serum C4 levels often correlate with HAE attacks. Treatment with Cinryze resulted in elevation of C4 levels at 12 hours. There was a statistically significant ($p = 0.0017$) difference in the changes in mean values from baseline between treatment groups at 12 hours, demonstrating the association of Cinryze treatment with an increase in C4 activity (Cinryze + 2.9 mg/dl versus placebo + 0.1 mg/dl).

Clinical efficacy and safety

Data from two randomised, double-blind, placebo-controlled studies (LEVP 2005-1/A and LEVP 2005-1/B), data from two open-label studies (LEVP 2006-1 and LEVP 2006-4) and 2 paediatric clinical studies (0624-203 and 0624-301) demonstrated the efficacy of Cinryze for the treatment and prevention of angioedema attacks in subjects with HAE.

Data from two observational studies (SHP616-401, IOS) that included subjects aged 8 to 83 years were consistent with the existing safety profile and no new safety concerns have been identified following exposure to Cinryze.

Cinryze for the treatment of HAE attacks

Study LEVP 2005-1/A used a randomised, double-blind, placebo-controlled, parallel group design; 71 subjects with acute HAE attacks were randomised (36 Cinryze, 35 placebo). The study demonstrated that treatment with Cinryze within 4 hours after the onset of an HAE attack resulted in a greater than 2-fold decrease in the time to beginning of unequivocal relief of the defining symptom of the HAE attack compared to placebo (median 2 hours for Cinryze vs. > 4 hours for placebo, $p = 0.048$). Treatment with Cinryze also resulted in a greater than 2-fold decrease in the time to complete resolution of the HAE attack compared to placebo (median 12.3 hours vs. 31.6 hours, $p = 0.001$). The percentage of subjects with beginning of unequivocal relief of the defining symptom within 4 hours after dosing was 60 % for Cinryze and 42 % for placebo ($p = 0.062$). Among 15 subjects treated with open-label Cinryze for laryngeal HAE attacks, none required intubation.

In open-label study LEVP 2006-1, 101 subjects were treated for a total of 609 acute HAE attacks (median 3 attacks per subject; range: 1 – 57). Within 4 hours after Cinryze dosing, 87 % of attacks achieved unequivocal relief of the defining symptom. For 95 % of attacks, clinical relief was observed and/or subjects were discharged to home within 4 hours. For subjects with > 1 attack, the proportion of attacks responding within 4 hours after Cinryze dosing and the time to response was comparable regardless of the number of attacks treated. Among 84 separate laryngeal HAE attacks, none required intubation following treatment with Cinryze.

Cinryze for the routine prevention of HAE attacks

Study LEVP 2005-1/B used a randomised, double-blind, placebo-controlled, crossover design; 22 subjects were evaluable for efficacy (randomised and treated in both crossover periods). The study demonstrated that prophylaxis with Cinryze resulted in a greater than 2-fold reduction in the number of HAE attacks compared to placebo (mean 6.3 attacks for Cinryze vs. 12.8 attacks for placebo, $p < 0.0001$). Angioedema attacks were also less severe during prophylactic Cinryze therapy compared to placebo (mean severity score 1.3 vs. 1.9 or a 32 % reduction, $p = 0.0008$) and of shorter duration (mean 2.1 days vs. 3.4 days or a 38 % reduction, $p = 0.0004$). The total number of days of swelling during prophylactic Cinryze therapy was reduced compared to placebo (mean 10.1 days vs. 29.6 days or a 66 % reduction, $p < 0.0001$). In addition, fewer open-label Cinryze infusions were required for treatment of HAE attacks during therapy with Cinryze compared to placebo (mean 4.7 infusions vs. 15.4 infusions or 70 % reduction, $p < 0.0001$).

In open-label study LEVP 2006-4, 146 subjects received Cinryze as HAE prophylaxis for periods ranging from 8 days to approximately 32 months (median 8 months). Prior to enrolment, subjects reported a median monthly HAE attack rate of 3.0 (range: 0.08 – 28.0); during therapy with

prophylactic Cinryze, this rate was 0.21 (range: 0 – 4.56), and 86 % of subjects experienced an average of ≤ 1 attack per month. For subjects receiving Cinryze prophylaxis for at least 1 year, the monthly attack rate per subject remained consistently low (0.34 attacks per month) relative to pre-study rates.

Cinryze for the pre-procedure prevention of HAE attacks

Open-label Cinryze was administered within 24 hours prior to a total of 91 medical, dental, or surgical procedures across the clinical programme (40 procedures in children and 51 procedures in adults). For 98 % of procedures, no HAE attacks were reported within the 72 hours after the Cinryze dose.

Paediatric population (age-group 6 – 11 years)

Cinryze for the treatment of HAE attacks

Study LEVP 2006-1: Twenty-two paediatric subjects were treated for 121 acute HAE attacks. The proportion of HAE attacks achieving unequivocal relief of the defining symptom within 4 hours after Cinryze treatment was comparable between the 22 children enrolled (age range: 2 – 17) and adults, with 89 % and 86 % of attacks achieving relief, respectively.

Study 0624-203: Nine subjects (age range: 6 – 11) were enrolled and received a single dose of Cinryze: 3 subjects (10 – 25 kg) received 500 Units(*); 3 subjects (> 25 kg) 1 000 Units(*), and 3 subjects (> 25 kg) 1 500 Units(*). All 9 (100 %) subjects achieved unequivocal beginning of relief of the defining symptom within 4 hours following initiation of treatment with Cinryze. Median interval was 0.5 hours (range: 0.25 – 2.5 hours): 1.25, 0.25, and 0.5 hours in the 500 Units(*), 1 000 Units(*), and 1 500 Units(*) Cinryze groups, respectively. Median interval to complete resolution of the HAE attack for the 9 subjects was 13.6 hours (range: 1.6 – 102.3 hours).

Cinryze for the prevention of HAE attacks

Study LEVP 2006-4: Prior to enrollment, 23 children (age range: 3 to 17 years) reported a median monthly HAE attack rate of 3.0 (range: 0.5 – 28.0). During the study while receiving Cinryze prophylaxis (1 000 Units(*) every 3 to 7 days; with the exception of a 3 year old child, receiving 500 Units(*) every 3 to 7 days), children in the various age subgroups experienced median monthly HAE attack rates of 0.4 (range: 0 – 3.4), and 87 % of children reported an average of ≤ 1 attack per month; these results were comparable to those observed in adults.

Study 0624-301: Six pediatric subjects (6 to 11 years of age) were enrolled and randomised to twice weekly dosing for 12 weeks in 2 treatment sequences (500/1 000 Units(*) or 1 000/500 Units(*) Cinryze). Both doses resulted in similar reduction of attack-frequency and showed clinical benefit regarding severity, duration, and requirement for acute treatment of attacks.

Paediatric population (age-group < 6 years)

For the 3 subjects less than 6 years, administration of Cinryze (500 Units(*) or 1 000 Units(*)) was associated with increases in C1-esterase inhibitor levels and clinical efficacy in acute treatment and prevention of attacks. Overall administration of Cinryze was well tolerated.

In all studies, administration of Cinryze resulted in increases in antigenic and functional C1-esterase inhibitor levels post-infusion compared to pre-infusion values in both children and adults.

5.2 Pharmacokinetic properties

A randomised, parallel group, open-label pharmacokinetic study of Cinryze was performed in subjects with non-symptomatic HAE. The subjects received either a single intravenous dose of 1 000 Units(*) or a 1 000 Units(*) dose followed by a second dose of 1 000 Units(*) 60 minutes later. The mean

pharmacokinetic parameters for functional human C1-esterase inhibitor derived from baseline-corrected concentration data are presented in Table 2.

Table 2 Mean Pharmacokinetic Parameters for Functional C1-esterase inhibitor Following Administration of Cinryze

Parameters	**Single Dose (1 000 Units*)**	**Double Dose (1 000 Units dose followed by a second 1 000 Units dose 60 minutes later)**
$C_{baseline}$ (U/ml)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C_{max} (U/ml)	0.68 ± 0.08 (n = 12)	0.85 ± 0.12 (n = 13)
Baseline-corrected C_{max} (U/ml)	0.37 ± 0.15 (n = 12)	0.51 ± 0.19 (n = 12)
t_{max} (hr) [median (range)]	[1.2 (0.3 – 26.0)] (n = 12)	[2.2 (1.0 – 7.5)] (n = 13)
$AUC_{(0-t)}$ (U*hr/ml)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
Baseline-corrected $AUC_{(0-t)}$ (U*hr/ml)	24.5 ± 19.1 (n = 12)	39.1 ± 20.0 (n = 12)
CL (ml/min)	0.85 ± 1.07 (n = 7)	1.17 ± 0.78 (n = 9)
Elimination half-life (hr)	56 ± 35 (n = 7)	62 ± 38 (n = 9)

n = number of subjects evaluated.
* Historically assigned potency values are expressed in in-house Units (U).

After intravenous administration of a single dose of Cinryze to HAE subjects, the serum concentration of functional C1-esterase inhibitor doubled within 1 to 2 hours. The maximum serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) appeared to increase from the single to double dose, although the increase was not dose-proportional. The mean elimination half-life of functional C1-esterase inhibitor after administration of Cinryze was 56 hours for a single dose and 62 hours for the double dose.

Because C1-esterase inhibitor is an endogenous human plasma protein, it 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 Cinryze are not expected to be altered by renal or hepatic impairment.

Paediatric population

Functional C1-esterase inhibitor activity was measured in children in the two open label studies (see section 5.1). Mean increases from baseline in functional C1-esterase inhibitor activity measured 1 hour post-dose in children 2 to < 18 years of age ranged from 20 % to 88 % in Study LEVP 2006-1 (treatment) and from 22 % to 46 % in Study LEVP 2006-4 (prevention) compared with 21 % to 66 % and 25 % to 32 % in adults, respectively. Two additional studies evaluated plasma levels in children (6 – 11 years).

In study 624-203, plasma C1-esterase inhibitor antigen and functional activity from 9 patients were obtained following a single IV dose of 500 Units(*), 1 000 Units(*), or 1 500 Units(*) Cinryze based on body weight (see section 5.1). Increases in C1-esterase inhibitor antigen levels and functional activity above the baseline values at 1 hour and 24 hours post-dose were demonstrated.

In Study 0624-301, plasma C1-esterase inhibitor antigen and functional activity were measured from 6 patients pre-dose and 1 h following IV administration of two dose levels of Cinryze (500 Units(*) and 1 000 Units(*)) every 3 or 4 days for 12 weeks. Both Cinryze doses resulted in relevant plasma levels of C1-esterase inhibitor antigen and functional activity.

5.3 Preclinical safety data

Cinryze contains as active ingredient C1-esterase inhibitor. It is derived from human plasma and acts like an endogenous constituent of plasma.

Non-clinical data reveal no special hazard for humans based on conventional studies of general toxicity and toxicity to reproduction. No genotoxicity studies were performed as the active substance is unlikely to interact directly with DNA or other chromosomal material. No studies on fertility, early embryonic and post-natal development, or carcinogenicity studies were conducted because chronic dosing in animals would be expected to be associated with development of neutralising antibodies to the human protein.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Sodium chloride
Sucrose
Sodium citrate
L-valine
L-alanine
L-threonine

Solvent:

Water for injections

6.2 Incompatibilities

Only use a silicone-free syringe (provided in the pack) for administration of the product.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

After reconstitution, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at room temperature (15 °C – 25 °C).

6.4 Special precautions for storage

Store below 25 °C. Do not freeze. Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

500 IU of human C1-esterase inhibitor in a colourless glass vial (Type I), closed with a rubber stopper (Type I) and an aluminium seal with a plastic flip-off cap.

5 ml of water for injections in a colourless glass vial (Type I), closed with a rubber stopper (Type I) and an aluminium seal with a plastic flip-off cap.

Each pack contains:
Two powder vials.
Two solvent vials.
2 filter transfer devices, 2 disposable 10 ml syringes, 2 venipuncture sets, and 2 protective mats.

6.6 Special precautions for disposal and other handling

Each kit contains material for either one 1 000 IU dose or two 500 IU doses.

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.

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 (15 ºC – 25 ºC).
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 centre 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 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*.

Administration process for a dose of 500 IU

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.

Administration process for a dose of 1 000 IU

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. 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER

EU/1/11/688/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 June 2011
Date of latest renewal: 26 May 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Prothya Biosolutions Netherlands B.V.
Plesmanlaan 125
1066 CX Amsterdam
The Netherlands

Baxalta US Inc.
4501 Colorado Boulevard
Los Angeles, CA 90039-1103
USA

Name and address of the manufacturers responsible for batch release

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

Shire International Licensing B.V.
Mercuriusplein 11
2132 HA Hoofddorp
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that all healthcare professionals who are expected to prescribe Cinryze are provided with an Educational pack.

The educational pack should contain the following:
- Summary of Product Characteristics and Patient Information Leaflet for Cinryze
- Educational material for healthcare professionals
- Educational materials for non-healthcare professionals

The educational material for healthcare professionals should include information on the following key elements:

- There are limited data on the use of this medicinal product in home or self-administration.

- It is the responsibility of the prescribing physician to determine which patients may be suitable for home or self-administration of Cinryze.

- It is the responsibility of the prescribing physician to provide appropriate training to the non-healthcare professional who will administer the treatment at home, such as the patient for self-administration or a family member. Regular review of the administration by the patient/carer needs to be performed to ensure maintenance of optimal practice.

- The training to be provided should address the following elements
  - Precaution for storage
  - Doses and Indications of treatment
  - Preparation of one dose of Cinryze (500 IU) by reconstituting one vial
  - Preparation of one dose of Cinryze (1 000 IU) by reconstituting two vials
  - Method of reconstitution of each vial
  - Technique of intravenous injection
  - Method and rate of administration of one dose of Cinryze (500 IU)
  - Method and rate of administration of one dose of Cinryze (1 000 IU)
  - Instruction to seek emergency treatment by health care professionals in case of failure to gain venous access or in case of lack of efficacy
  - Instruction in handling possible adverse reactions

Information on the need to keep a diary to document each treatment received at home and to bring it at each visit. The information collected should include:

- Date and time of treatment
- Batch number and dose received
- Indication for treatment (acute attack or prophylaxis)
- Response to treatment
- Any adverse reactions

- It is the responsibility of the prescribing physician to verify that all the necessary skills have been acquired by the non-healthcare professional and that Cinryze may be safely and effectively administered at home.

The educational material for non-healthcare professionals should include information on the following key elements:

- There are limited data on the use of this medicinal product in home or self-administration.

- For some patients the prescribing physician may decide that Cinryze may be administered at home by a non-healthcare professional such as a family member or by self-administration.

- Necessary skills have to be acquired by non-healthcare professionals before Cinryze may be safely and effectively administered at home.

- Their prescribing physician will provide training on the following elements:
  - Precaution for storage
  - Doses and indications of treatment
  - Preparation of one dose of Cinryze (500 IU) by reconstituting one vial
  - Preparation of one dose of Cinryze (1 000 IU) by reconstituting two vials
  - Method of reconstitution of each vial
  - Technique of intravenous injection
  - Method and rate of administration of one dose of Cinryze (500 IU)
  - Method and rate of administration of one dose of Cinryze (1 000 IU)
  - Instruction to seek emergency treatment by health care professionals in case of failure to gain venous access or in case of lack of efficacy
  - Instruction in handling possible adverse reactions
  - Information on the need to keep a diary to document each treatment received at home and to bring it at each visit. The information collected should include:
  - Date and time of treatment
  - Batch number and dose received
  - Indication for treatment (acute attack or prophylaxis)
  - Response to treatment
  - Any adverse reactions
  - A leaflet providing detailed information on the key elements of the training that should be kept at home for further reference.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cinryze 500 IU powder and solvent for solution for injection
human C1-esterase inhibitor

2. STATEMENT OF ACTIVE SUBSTANCE

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 are combined for a single dose.

3. LIST OF EXCIPIENTS

Powder vial: sodium chloride, sucrose, sodium citrate, L-valine, L-alanine, L-threonine
Solvent vial: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

2 powder vials
2 solvent vials
2 filter transfer devices
2 disposable 10 ml syringes
2 venipuncture sets
2 protective mats

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 ºC. Do not freeze. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/11/688/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cinryze

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CINRYZE VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Cinryze 500 IU powder for solution for injection
human C1-esterase inhibitor
IV Use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Cinryze
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cinryze 500 IU powder and solvent for solution for injection
human C1-esterase inhibitor

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaftlet. See section 4.

What is in this leaflet

1. What Cinryze is and what it is used for

Cinryze contains the human protein called “C1-esterase inhibitor” as the active substance.

C1-esterase inhibitor is a naturally occurring protein that is normally present in the blood. If you have a low amount of C1-esterase inhibitor in your blood or your C1-esterase inhibitor is not working properly, this can lead to swelling attacks (called angioedema). Symptoms may include stomach pains and swelling of the:

- hands and feet
- face, eyelids, lips or tongue
- voice-box (larynx), which may make breathing difficult
- genitals

In adults and children, Cinryze can raise the amount of C1-esterase inhibitor in the blood and either prevent (prior to undergoing medical or dental procedures) these swelling attacks from occurring or stop swelling attacks once they have begun.

In adults, adolescents and children (aged 6 years and above), Cinryze can raise the amount of C1-esterase inhibitor in the blood and routinely prevent swelling attacks from occurring.

2. What you need to know before you take Cinryze

Do not take Cinryze

- If you are allergic to human C1-esterase inhibitor or any of the other ingredients of this medicine (listed in section 6). It is important to tell your doctor if you think you have ever had an allergic reaction to any of the ingredients in Cinryze.

Warnings and precautions

- Before you start treatment with Cinryze, it is important that you tell your doctor if you have, or have had, problems with your blood clotting (thrombotic events). You will be carefully monitored if this is the case.
- If you begin to suffer from rashes, tightness of the chest, wheezing, or a fast heartbeat once you have taken Cinryze, you should tell your doctor immediately (see section 4).
- When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
- The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B and hepatitis C viruses, and for the non-enveloped hepatitis A and parvovirus B19 viruses.
- Your doctor may recommend that you consider having vaccinations against hepatitis A and B if you regularly or repeatedly receive human C1-esterase inhibitor products that have been taken from human plasma.
- In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded by your nurse or doctor.

Children

Cinryze is not for use in children below 6 years of age for routine prevention of angioedema attacks.

Other medicines and Cinryze

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking Cinryze. There is limited information on the safety of Cinryze use during pregnancy and breast-feeding. Your doctor will discuss with you the risks and benefits of taking this medicine.

Driving and using machines

Cinryze has minor influence on the ability to drive and use machines.

Cinryze contains sodium

This medicine contains 11.5 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.5 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Cinryze

Your treatment will be initiated and managed under supervision of a doctor experienced in the care of patients with hereditary angioedema (HAE).

A doctor or nurse may prepare and inject Cinryze for you. If your doctor decides you can self-administer, your doctor or nurse will train you or a family member to prepare and inject Cinryze. Your doctor will regularly review the preparation and administration process with you or a family member or caregiver.

The recommended dose of Cinryze for adults, adolescents, children, the elderly, or patients suffering from kidney or liver problems is as follows:

Use in adults and adolescents (12 years and above)

Treatment of swelling attacks

- A dose of 1 000 IU (two vials) of Cinryze should be injected at the first sign of a swelling attack.
- A second injection of 1 000 IU may be given if your symptoms do not improve after 60 minutes.
- If you are experiencing a severe attack, particularly a swelling of the voice-box (larynx), or if initiation of treatment is delayed, the second 1 000 IU dose may be given earlier than 60 minutes after the first dose, depending on your clinical response.
- Cinryze should be injected intravenously (into the vein).

Routine prevention of swelling attacks

- A dose of 1 000 IU (two vials) of Cinryze should be injected every 3 or 4 days for routine prevention of swelling attacks.
- The dosing interval may be adjusted by your doctor depending upon your response to Cinryze.
- Cinryze should be injected intravenously (into the vein).

Prevention of swelling attacks prior to surgery

- A dose of 1 000 IU (two vials) of Cinryze should be injected up to 24 hours before a medical, dental, or surgical procedure.
- Cinryze should be injected intravenously (into the vein).

Use in children

Treatment of angioedema attacks	**Pre-procedure prevention of angioedema attacks**	**Routine prevention of angioedema attacks**
2 to 11 years, > 25 kg: A dose of 1 000 IU (two vials) of Cinryze should be injected at the first sign of a swelling attack. A second injection of 1 000 IU may be given if your symptoms do not improve after 60 minutes.	*2 to 11 years, > 25 kg:* A dose of 1 000 IU (two vials) of Cinryze should be injected up to 24 hours before a medical, dental, or surgical procedure.	*6 to 11 years:* A dose of 500 IU (one vial) of Cinryze should be injected every 3 or 4 days for routine prevention of swelling attacks. The dosing interval may be adjusted by your doctor depending upon your response to Cinryze.

2 to 11 years, 10 – 25 kg: A dose of 500 IU (one vial) of Cinryze should be injected at the first sign of a swelling attack. A second injection of 500 IU may be given if your symptoms do not improve after 60 minutes.	*2 to 11 years, 10 – 25 kg:* A dose of 500 IU (one vial) of Cinryze should be injected up to 24 hours before a medical, dental, or surgical procedure.	

Reconstitution and method of administration

Cinryze is usually injected into a vein (intravenously) by your doctor or nurse. You or your caregiver might also administer Cinryze as an injection, but only after receiving adequate training. If you are injecting Cinryze yourself, always use it exactly as your doctor has instructed you. Check with your doctor if you are not sure. If your doctor decides that you may be suitable for such home-treatment, he/she will give you detailed instructions. You will be required to keep a diary in order to document each treatment received at home and to bring it to each of your visits to the doctor. Regular review of your/your caregiver's injection technique will be performed to ensure continued appropriate handling.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This can include allergic-type reactions.

Tell your doctor **immediately** if you experience any of the following symptoms after taking this medicine. Although they are rare, the symptoms can be severe.

Sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body).

Very common side effects (may affect more than 1 in 10 people): headache, nausea.

Common side effects (may affect up to 1 in 10 people): hypersensitivity, dizziness, vomiting, rash, itching or redness, injection site rash or pain, fever.

Uncommon side effects (may affect up to 1 in 100 people): high blood sugar, blood clot, painful veins, hot flush, cough, stomach pain, diarrhoea, skin flaking, joint swelling and pain, muscle pain, and chest discomfort.

Side effects in children and adolescents are expected to be similar to those in adults.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cinryze

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vials after "EXP". Store below 25 °C. Do not freeze. Store in the original package in order to protect from light.

Once reconstituted, Cinryze solution should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cinryze contains

The active substance is human C1-esterase inhibitor produced from the plasma of human donors. Each powder vial contains 500 IU of human C1-esterase inhibitor. 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.

The total protein content of the reconstituted solution is 15 ± 5 mg/ml.

One International Unit (IU) is equivalent to the amount of C1-esterase inhibitor present in 1 ml of normal human plasma.

The other ingredients are sodium chloride, sucrose, sodium citrate, L-valine, L-alanine and L-threonine (see section 2).

Solvent: water for injections.

What Cinryze looks like and contents of the pack

Powder and solvent for solution for injection.
Cinryze is a white powder contained in a vial.
After it has been dissolved in the water for injections the solution is clear and colourless to slightly blue.

Each pack contains:
2 vials of Cinryze 500 IU powder for solution for injection
2 vials of water for injections (5 ml each)
2 filter transfer devices
2 disposable 10 ml syringes
2 venipuncture sets
2 protective mats

Only use a silicone-free syringe (provided in the pack) for administration of the product.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

Manufacturer

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

Shire International Licensing B.V.
Mercuriusplein 11
2132 HA Hoofddorp
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

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.

Only use a silicone-free syringe (provided in the pack) for administration of the product.

Preparation and handling

Cinryze is intended for intravenous administration (into the vein) after reconstitution with water for injections.
Cinryze vial is for single use only.

Reconstitution

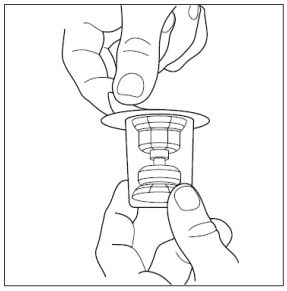
For a dose of 500 IU: One powder vial, 1 solvent vial, 1 filter transfer device, 1 disposable 10 ml syringe, 1 venipuncture set and 1 protective mat are needed. Store the remaining vial and administration equipment for the next dose.

For a dose of 1 000 IU: Two powder vials, 2 solvent vials, 2 filter transfer devices, 1 disposable 10 ml syringe, 1 venipuncture set and 1 protective mat are needed.

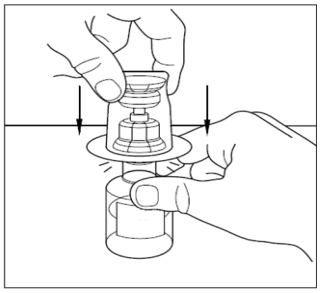
Each product vial should be reconstituted with 5 ml water for injections.
One vial of reconstituted Cinryze corresponds to a dose of 500 IU. Therefore only reconstitute one vial of Cinryze for one dose of 500 IU.

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 (15 ºC – 25 ºC).
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.

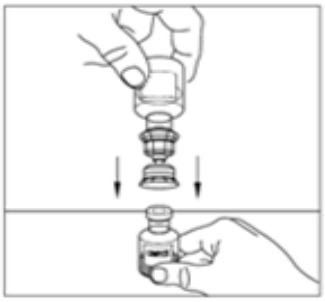


8. Note: the transfer device must be attached to the solvent vial before being attached to the powder vial, so that the vacuum in the powder vial is not lost. Place the solvent vial on a flat surface and insert the blue end of the transfer device into the solvent vial, pushing down until the spike penetrates through the centre 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.



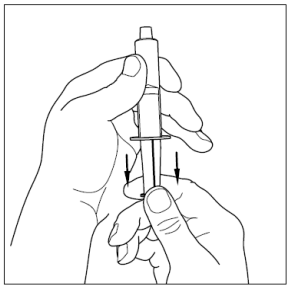
11. Gently swirl the powder vial until all powder is dissolved. Do not shake the powder vial. Make sure all the powder is completely dissolved.

12. Disconnect the solvent vial by turning it anti-clockwise. Do 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.

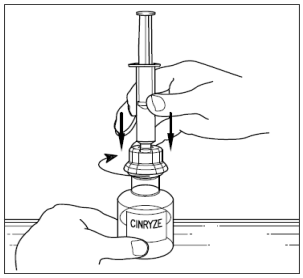
Two vials of Cinryze powder must be reconstituted to make one dose (1 000 IU/10 ml). Therefore repeat instructions 1 to 12 above using an additional package containing a transfer device to reconstitute the second of two powder vials. Do not reuse the transfer device. Once the two vials are reconstituted proceed to administration process for a dose of 1 000 IU.

Administration process for a dose of 500 IU

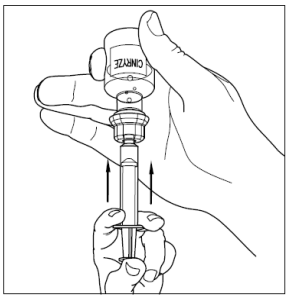
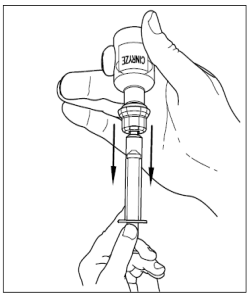
1. Aseptic technique should be used during the administration procedure.
2. After reconstitution, the Cinryze solutions are colourless to slightly blue and clear. Do not use the product if the solutions are turbid or discoloured.
3. Using a sterile, disposable 10 ml syringe, draw back the plunger to allow approximately 5 ml of air into the syringe.



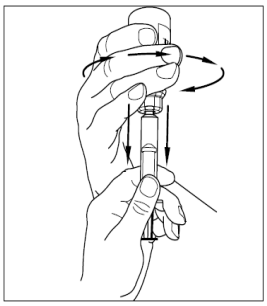
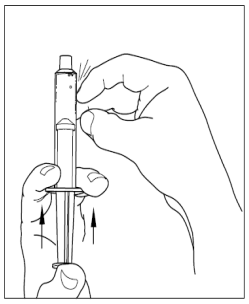
4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise.



5. Invert the vial gently and inject air into the solution and then slowly withdraw the reconstituted Cinryze solution into the syringe.

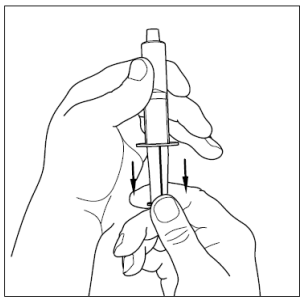
6. Detach the syringe from the vial by turning it anti-clockwise and releasing it from the clear end of the transfer device.

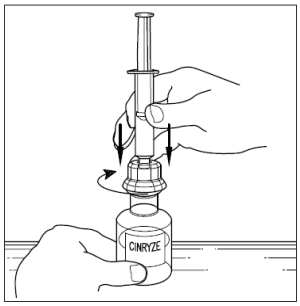
7. Inspect the reconstituted Cinryze solution for particulate matter prior to administration; do not use if particles are observed.
8. Attach the venipuncture set to the syringe containing Cinryze solution and inject intravenously (into the vein) into the patient. Administer 500 IU (reconstituted in 5 ml of water for injections) of Cinryze by intravenous injection at a rate of 1 ml per minute over 5 minutes.

Administration process for a dose of 1 000 IU

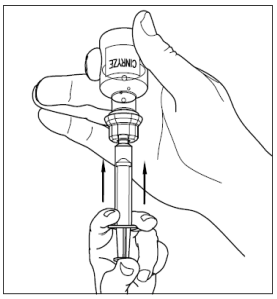
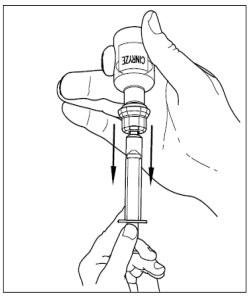
1. Aseptic technique should be used during the administration procedure.
2. After reconstitution, the Cinryze solutions are colourless to slightly blue and clear. Do not use the product if the solutions are turbid or discoloured.
3. Using a sterile, disposable 10 ml syringe, draw back the plunger to allow approximately 5 ml of air into the syringe.



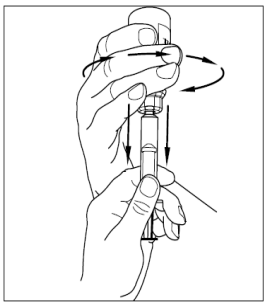
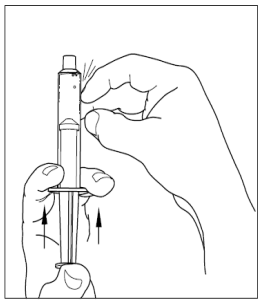
4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise.



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. 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 vein) into the patient. Administer 1 000 IU (reconstituted in 10 ml of water for injections) of Cinryze by intravenous injection (into the vein) at a rate of 1 ml per minute over 10 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.