

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Cinryze 500 Units powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: C1 inhibitor (human)

Each single-use powder vial contains 500 Units of C1 inhibitor (human)<sup>1</sup>.

After reconstitution, one vial contains 500 Units of C1 inhibitor (human) per 5 ml corresponding to a concentration of 100 Units/ml. One Unit is equivalent to the mean quantity of C1 inhibitor present in 1 ml of normal human plasma.

The total protein content of the reconstituted solution is  $15 \pm 5$  mg/ml.

### Excipients

The product contains up to 41 mg of sodium per dose (i.e. in 10 ml).

For a full list of excipients, see section 6.1.

<sup>1</sup> produced from the plasma of human donors

## 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 and adolescents with hereditary angioedema (HAE).

Routine prevention of angioedema attacks in adults and adolescents 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

- 1000 Units of Cinryze at the first sign of the onset of an acute attack.
- A second dose of 1000 Units may be administered if the patient has not responded adequately after 60 minutes.

- For patients experiencing severe attacks particularly laryngeal attacks or if initiation of treatment is delayed, the second dose can be given sooner than 60 minutes.

#### Routine prevention of angioedema attacks

- 1000 Units 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

- 1000 Units of Cinryze within 24 hours before a medical, dental, or surgical procedure.

#### *Paediatric population*

For treatment, routine prevention and pre-procedure prevention in adolescents the dose is the same as for adults.

The safety and efficacy of Cinryze in children before adolescence has not yet been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on posology can be made.

#### *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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

The reconstituted product should be administered by intravenous injection at a rate of 1 ml per minute.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

### **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 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.

#### *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.

It is strongly recommended that every time Cinryze is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the 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 drug 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 inhibitor product (up to 500 Units/kg) to prevent capillary leak syndrome.

#### *Sodium*

Cinryze contains up to 41 mg sodium per 10 ml solution. To be taken into consideration by patients on a controlled sodium diet.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been conducted.

### **4.6 Fertility, pregnancy and lactation**

#### *Pregnancy*

Data on a limited number of exposed pregnancies indicate no adverse effects of C1 inhibitor on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. No maternal or embryofetal effects of treatment were observed in reproductive studies in rats at dose levels up to 28-times the recommended human dose (1000 Units) based on an average adult body weight of 70 kg. The potential risk for humans is unknown.

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

#### *Breast-feeding*

It is unknown whether C1 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 only common adverse reaction observed following Cinryze infusion in clinical studies was rash; descriptions of rash characteristics were non-specific, but were typically described as involving the upper extremities, chest, abdomen, or injection site. None of the rashes were serious, and none led to discontinuation of medicinal product.

#### *Tabulated list of adverse reactions*

Adverse reaction frequency was estimated primarily based on summation of unique Cinryze-related adverse events reported across 8 completed clinical studies in HAE subjects. This includes data from two placebo-controlled studies, three open-label studies, and three compassionate-use subjects. There were a total of 385 subject exposures involving over 14,500 infusions of Cinryze in these studies.

Adverse reactions with suspected relationship (i.e. determined by the investigator to be possibly, probably, or definitely related) 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), and very rare ( $< 1/10,000$ ).

Table 1. Adverse Reactions with Suspected Relationship to Cinryze Reported in Clinical Studies by Investigators

<b>System Organ Class</b>	<b>Frequency:</b>	<b>Adverse reaction</b>
Metabolism and nutrition disorders	Uncommon:	Hyperglycaemia
Nervous system disorders	Uncommon:	Dizziness, headache
Vascular disorders	Uncommon:	Venous thrombosis, phlebitis, venous burning, hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon:	Cough
Gastrointestinal disorders	Uncommon:	Nausea, vomiting, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Common: Uncommon:	Rash Contact dermatitis, erythema, pruritus
Musculoskeletal and connective tissue disorders	Uncommon:	Joint swelling, arthralgia, myalgia
General disorders and administration site conditions	Uncommon:	Injection site rash/erythema, infusion site pain, chest discomfort, pyrexia

#### *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 8 completed clinical studies, there were 46 unique paediatric subjects enrolled and exposed to Cinryze (2-5 years, n=3; 6-11 years, n=17; 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 and adults.

### *Post-Marketing Data*

In post-marketing safety surveillance since 2008, no new safety issues have been identified.

For safety with respect to transmissible agents, see section 4.4.

## **4.9 Overdose**

No case of overdose has been reported.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antihemorrhagics, proteinase inhibitors, C1 inhibitor, ATC-code: B02AB03.

#### *Mechanism of action*

C1 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 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 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 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 inhibitor within 1 hour after administration. Administration of C1 inhibitor increases serum levels of C1 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*

Two randomised, double-blind, placebo-controlled studies (LEVP 2005-1/A and LEVP 2005-1/B) and data from two open-label studies (LEVP 2006-1 and LEVP 2006-4) demonstrated the efficacy of Cinryze for the treatment and prevention of angioedema attacks in subjects with C1 inhibitor deficiency.

### 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 enrollment, 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  $\leq 1$  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*

Treatment (LEVP 2006-1): 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. Prevention (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, 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  $\leq 1$  attack per month; these results were comparable to those observed in adults.

In both studies LEVP 2006-1 and LEVP 2006-4, administration of Cinryze resulted in increases in antigenic and functional C1 inhibitor levels post-infusion compared to pre-infusion values, with similar trends observed in children and adults.

The European Medicines Agency has deferred the obligation to submit the results of two of four studies with Cinryze, in the paediatric population, in C1 inhibitor deficiency. See section 4.2 for information on paediatric use.

## 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 1000 Units or a 1000 Units dose followed by a second dose of 1000 Units 60 minutes later. The mean pharmacokinetic parameters for functional C1 inhibitor derived from baseline-corrected concentration data are presented in Table 2.

Table 2. Mean Pharmacokinetic Parameters for Functional C1 Inhibitor Following Administration of Cinryze

<b>Parameters</b>	<b>Single Dose (1000 Units*)</b>	<b>Double Dose (1000 Units dose followed by a second 1000 Units dose 60 minutes later)</b>
C <sub>baseline</sub> (U/ml)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C <sub>max</sub> (U/ml)	0.68 ± 0.08 (n = 12)	0.85 ± 0.12 (n = 13)
Baseline-corrected C <sub>max</sub> (U/ml)	0.37 ± 0.15 (n=12)	0.51 ± 0.19 (n=12)
t <sub>max</sub> (hr) [median (range)]	[1.2 (0.3 – 26.0)] (n = 12)	[2.2 (1.0 – 7.5)] (n = 13)
AUC <sub>(0-t)</sub> (U*hr/ml)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
Baseline-corrected AUC <sub>(0-t)</sub> (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.

\*One Unit is equal to the mean quantity of C1 inhibitor present in 1 ml of normal human plasma.

After intravenous administration of a single dose of Cinryze to HAE subjects, the serum concentration of functional C1 inhibitor doubled within 1 to 2 hours. The maximum serum concentration (C<sub>max</sub>) 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 inhibitor after administration of Cinryze was 56 hours for a single dose and 62 hours for the double dose.

Because C1 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 inhibitor activity was measured in children in the two open label studies (see section 5.1). Mean increases from baseline in functional C1 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.

### **5.3 Preclinical safety data**

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**

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

### **6.3 Shelf life**

3 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 and transport refrigerated (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

500 Units of C1 inhibitor in a colourless glass vial (Type I), sealed 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.

Administration set: 2 filter transfer devices, 1 disposable 10 ml syringe, 1 venipuncture set, 2 disinfection swabs, 1 protective mat.

## **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.

#### *Reconstitution*

Each product vial should be reconstituted with 5 ml water for injections. Two vials of reconstituted Cinryze are combined for ONE dose (1000 Units).

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. Bring the powder vial and the solvent vial to room temperature (15°C - 25°C).
4. Remove plastic caps from the powder and solvent vials.
5. Cleanse stoppers with an alcohol wipe and allow them to dry prior to use.
6. Remove protective covering from the top of the transfer device package. Do not remove the device from the package.
7. 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.
8. Remove the plastic package from the transfer device and discard it. Take care not to touch the exposed end of the transfer device.
9. 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.
10. Gently swirl the powder vial until all powder is dissolved. Do not shake the powder vial. Make sure all the powder is completely dissolved.
11. 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 Units of C1 inhibitor in 5 ml, resulting in a concentration of 100 Units/ml.

TWO vials of Cinryze powder must be reconstituted to make one dose (1000 Units/10 ml). Therefore, repeat instructions 1 to 11 above using an additional package containing a transfer device to reconstitute the second of two powder vials. Do not reuse the transfer device.

#### *Administration process*

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 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 4 to 7 with a second vial of reconstituted Cinryze to make one complete 10 ml dose.
8. Attach a needle to the syringe containing Cinryze solution and inject intravenously into the patient. Administer 1000 Units (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.

#### **7. MARKETING AUTHORISATION HOLDER**

ViroPharma SPRL  
Rue Montoyer 47  
B - 1000 Brussels  
Belgium

#### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/11/688/001

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

15 June 2011

#### **10. DATE OF REVISION OF THE TEXT**

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

**ANNEX II**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND  
MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH  
RELEASE**

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A. Manufacturer of the biological active substance and manufacturing authorisation holder responsible for batch release**

Name and address of the manufacturer of the biological active substance

Sanquin Blood Supply Foundation  
Plesmanlaan 125  
NL-1066 CX Amsterdam  
The Netherlands

Name and address of the manufacturer responsible for batch release

Sanquin Blood Supply Foundation  
Plesmanlaan 125  
NL-1066 CX Amsterdam  
The Netherlands

**B. Conditions of the marketing authorisation**

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

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

- **Conditions or restrictions with regard to the safe and effective use of the medicinal product**
- 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 (1000 Units) by reconstituting two vials

Method of reconstitution of each vial

Technique of intravenous injection

Method and rate of administration of one dose of Cinryze (1000 Units)

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 drug 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 existence of a post marketing registry in which health care professionals are encouraged to enter patients

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 (1000 Units) by reconstituting two vials

Method of reconstitution of each vial

Technique of intravenous injection

Method and rate of administration of one dose of Cinryze (1000 Units)

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 drug 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.

- **Other conditions**
- To ensure the continuous consistency of the potency and purity of the finished product, the applicant should fulfil the following conditions:
- to calibrate an in-house concentrate standard against the WHO 1st International Standard for C1-inhibitor, concentrate NIBSC code: 08/256 not later than Q4 2011. A retest period should be defined once the reference material is calibrated against the international standard. A new in-house control lot for potency that is representative of the current finished product has to be implemented by Q4 2011.
- to tighten the finished product specifications for C1 inhibitor activity, for specific activity, and for pH. The adjustment should be based on a statistically significant number of historical and commercial Cinryze batches representative of the current manufacturing process. The specifications have to be implemented by Q4 2011.
- to add a release specification to the finished product for purity of C1 inhibitor protein, determined by a validated, quantitative assay. The specification has to be implemented by Q4 2011.
- to add specifications for the recently identified impurities C3 protease precursor and alpha-1-antichymotrypsin. The new specifications should be implemented in conjunction with the introduction of the 1st I. S. for C1 inhibitor, by Q4 2011.
- A post-marketing registry should be set-up with the objective to gain additional information on the safety and the use of Cinryze in the EU. Further information to be collected includes data on drug exposure, adverse drug reactions, frequency of attacks, long-term safety data, use in pregnant patients with outcome of pregnancies, as well as use in the paediatric population. Particular attention should be given to the monitoring of cases of severe and laryngeal attacks as well as cases where treatment started later than 4 hours after onset of attack; details about the administered dose, timing of dosing, safety and efficacy outcome should be reported. Data collected in this registry should be reported to the CHMP at the time of PSUR submissions. A protocol for the registry should be submitted to the CHMP for agreement within 2 months of the Commission Decision granting the Marketing Authorisation or prior to marketing, whichever is soonest. The MAH shall submit to the Agency an Updated Risk Management Plan to take into account this measure within one month after the protocol is agreed.

#### Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described and presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

#### Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached

At the request of the EMEA

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Cinryze 500 Units powder and solvent for solution for injection  
C1 inhibitor (human)

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

After reconstitution, one vial contains 500 Units of C1 inhibitor (human) per 5 ml corresponding to a concentration of 100 Units/ml. Two vials of reconstituted Cinryze are combined for a single dose.

The total protein content of the reconstituted solution is  $15 \pm 5$  mg/ml.

**3. LIST OF EXCIPIENTS**

Powder vial - other ingredients: 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 each containing 5 ml water for injections

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use.  
Read the package leaflet before use

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store and transport refrigerated (2°C - 8°C). Do not freeze. Store in 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 product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

ViroPharma SPRL  
Rue Montoyer 47  
B - 1000 Brussels  
Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/11/688/001

**13. BATCH NUMBER**

BN

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Cinryze

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**CINRYZE VIAL LABEL**

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

Cinryze 500 Units powder for solution for injection  
C1 inhibitor (human)  
IV Use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

BN

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

500 Units

**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**

BN

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 ml

**6. OTHER**

**B. PACKAGE LEAFLET**

## **PACKAGE LEAFLET: INFORMATION FOR THE USER**

### **Cinryze 500 Units powder and solvent for solution for injection** C1 inhibitor (human)

#### **Read all of this leaflet carefully before you start taking this medicine.**

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Cinryze is and what it is used for
2. Before you take Cinryze
3. How to take Cinryze
4. Possible side effects
5. How to store Cinryze
6. Further information

### **1. WHAT CINRYZE IS AND WHAT IT IS USED FOR**

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

C1 inhibitor is a naturally occurring protein that is normally present in the blood. If you have a low amount of C1 inhibitor in your blood or your C1 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 adolescents, Cinryze can raise the amount of C1 inhibitor in the blood and either prevent these swelling attacks from occurring or stop swelling attacks once they have begun.

### **2. BEFORE YOU TAKE CINRYZE**

#### **Do not take Cinryze**

- If you are allergic (hypersensitive) to C1 inhibitor or any of the other ingredients of Cinryze (see section 6, “Further information”). It is important to tell your doctor if you think you have ever had an allergic reaction to any of the ingredients in Cinryze.

#### **Take special care with Cinryze**

- 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 heart beat once you have taken Cinryze, you should tell your doctor **immediately**.

- 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 C1 inhibitor products that have been taken from human plasma.

It is strongly recommended that every time you receive a dose of Cinryze the name and batch number of the product are recorded by your nurse or doctor in order to maintain a record for the batches used.

### **Children**

Cinryze is not for use in children before adolescence.

### **Taking Cinryze with other medicines**

Always tell your doctor about other medicines you are taking or have recently taken, including those bought without a prescription.

### **Pregnancy and breast-feeding**

If you think you might be pregnant, are planning to get pregnant, or are breast-feeding, 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**

No studies on the effects of the medicine on driving or using machines have been performed.

### **Important information about some of the ingredients of Cinryze**

This medicine contains up to 41 mg of sodium in the recommended 10 ml dose. This should be taken into account by people on a controlled sodium diet.

## **3. HOW TO TAKE CINRYZE**

A doctor or nurse may prepare and inject Cinryze for you.

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

### **Treatment of swelling attacks**

- A dose of 1000 Units of Cinryze should be injected at the first sign of a swelling attack.

- A second injection of 1000 Units may be given if your symptoms do not improve after 60 minutes.
- If you are experiencing a severe attack, particularly a laryngeal attack, or if initiation of treatment is delayed, the second 1000 Units dose may be given earlier than 60 minutes after the first dose, depending on your clinical response.
- Cinryze should be injected intravenously.

#### **Prevention of swelling attacks**

- A dose of 1000 Units 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.

#### **Prevention of swelling attacks prior to surgery**

- A dose of 1000 Units of Cinryze should be injected up to 24 hours before a medical, dental, or surgical procedure.
- Cinryze should be injected intravenously.

#### **Reconstitution and method of administration**

Cinryze is usually injected into a vein (intravenously) by your doctor or nurse. You or your carer might also administer Cinryze as an injection, but only after receiving adequate training. 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 carer's injection technique will be performed to ensure continued appropriate handling.

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

#### **4. POSSIBLE SIDE EFFECTS**

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

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).

The frequency of possible side effects listed below is defined using the following convention:

- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)
- not known (frequency cannot be estimated from the available data).

Common side effects: rash.

Uncommon side effects: high blood sugar, dizziness, headache, blood clot, painful veins, hot flush, cough, nausea, vomiting, stomach pain, diarrhoea, skin flaking, itching or redness, joint swelling and pain, muscle pain, injection site rash or pain, chest discomfort, and fever.

**If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

## **5. HOW TO STORE CINRYZE**

Keep out of the reach and sight of children.

Do not use Cinryze after the expiry date which is stated on the carton or vials after "EXP". Store and transport refrigerated (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

Once reconstituted, Cinryze solution should be used immediately.

Medicines must not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## **6. FURTHER INFORMATION**

### **What Cinryze contains**

The active substance is C1 inhibitor produced from the plasma of human donors. Each powder vial contains 500 units of C1 inhibitor. After reconstitution, one vial contains 500 Units (U) of C1 inhibitor (human) per 5 ml. Two vials of reconstituted Cinryze are combined for a single dose, corresponding to a concentration of 100 U/ml.

The total protein content of the reconstituted solution is  $15 \pm 5$  mg/ml.

One Unit is equivalent to the mean quantity of C1 inhibitor present in 1 ml of normal human plasma.

The other ingredients (excipients) are:

Powder vial: sodium chloride, sucrose, sodium citrate, L-valine, L-alanine and L-threonine.

Solvent vial: water for injections.

### **What Cinryze looks like and contents of the pack**

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 of Cinryze contains:

2 vials of Cinryze 500 Units powder for solution for injection

2 vials of water for injections (5 ml each)

The administration set contains:

2 filter transfer devices

1 disposable 10 ml syringe

1 venipuncture set

2 disinfection swabs

1 protective mat

**Marketing Authorisation Holder:**

ViroPharma SPRL  
Rue Montoyer 47  
B - 1000 Brussels Belgium

**Manufacturer:**

Sanquin Blood Supply Foundation  
Plesmanlaan 125  
1066 CX Amsterdam  
The Netherlands

**This leaflet was last approved in 06/2011.**

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

The following information is intended for medical or 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.

#### *Preparation and handling*

Cinryze is intended for intravenous administration after reconstitution with water for injections. Cinryze vial is for single use only.

#### *Reconstitution*

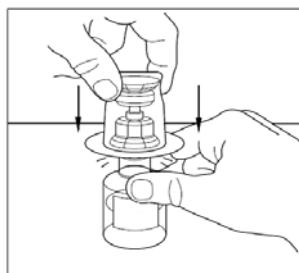
Each product vial should be reconstituted with 5 ml water for injections.

Two vials of reconstituted Cinryze are combined for ONE dose (1000 Units).

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. Bring the powder vial and the solvent vial to room temperature (15°C - 25°C).
4. Remove plastic caps from the powder and solvent vials.
5. Cleanse stoppers with an alcohol wipe and allow them to dry prior to use.
6. Remove protective covering from the top of the transfer device package. Do not remove the device from the package.



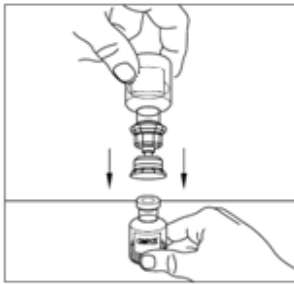
7. Note: the transfer device must be attached to the solvent vial before being attached to the powder vial, so that the vacuum in the powder vial is not lost. Place the solvent vial on a flat surface and insert the blue end of the transfer device into the solvent vial, pushing down until the spike penetrates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



8. Remove the plastic package from the transfer device and discard it. Take care not to touch the exposed end of the transfer device.



9. 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.



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



11. Disconnect the solvent vial by turning it anti-clockwise. Do not remove the clear end of the transfer device from the powder vial.

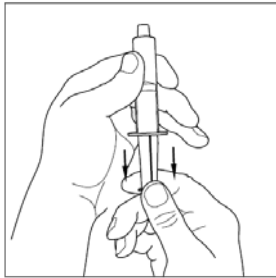


ONE vial of reconstituted Cinryze contains 500 Units of C1 inhibitor in 5 ml, resulting in a concentration of 100 Units/ml.

TWO vials of Cinryze powder must be reconstituted to make one dose (1000 Units/10 ml). Therefore repeat instructions 1 to 11 above using an additional package containing a transfer device to reconstitute the second of two powder vials. Do not reuse the transfer device.

*Administration process*

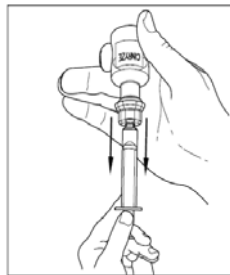
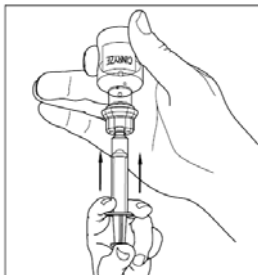
1. Aseptic technique should be used during the administration procedure.
2. After reconstitution, the Cinryze solutions are colourless to slightly blue and clear. Do not use the product if the solutions are turbid or discoloured.
3. Using a sterile, disposable 10 ml syringe, draw back the plunger to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



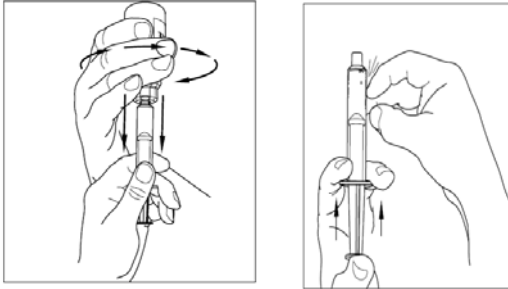
4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise.



5. Invert the vial 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 4 to 7 with a second vial of reconstituted Cinryze to make one complete 10 ml dose.
8. Attach a needle to the syringe containing Cinryze solution and inject intravenously into the patient. Administer 1000 Units (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.