PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

CINRYZE®*

C1 esterase inhibitor (human)

500 IU Powder for Solution/vial, reconstituted with 5 mL of diluent for intravenous injection

ATC code: B06AC01

Complement Inhibitors

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RECENT MAJOR LABEL CHANGES

All Sections, Conversion to June 2017 Template, DEC, 2020

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CINRYZE® (C1 esterase inhibitor [human]) is indicated for:

- Routine prevention of angioedema attacks in adults and adolescents with hereditary angioedema (HAE).

1.1 Pediatrics

The safety and effectiveness of CINRYZE have not been established in children. A total of 46 subjects who have received CINRYZE in the clinical trials were under 18 years of age (3 were less than 6 years of age, 17 were between 6 to 11 years of age, and 26 were between 12 to 17 years of age).

1.2 Geriatrics

No special investigations have been performed.

2 CONTRAINDICATIONS

CINRYZE is contraindicated in patients who have manifested life-threatening immediate hypersensivity reactions, including anaphylaxis, to the product, or who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

A healthcare practitioner, caregiver or patient can administer CINRYZE. The decision on the use of home-treatment for an individual patient should be made by a healthcare practitioner. Appropriate training must be provided by the healthcare practitioner prior to a caregiver or patient administering CINRYZE.

A patient should not attempt to self-administer unless trained by a healthcare provider.

3.2 Recommended Dose and Dosage Adjustment

Routine prevention of angioedema attacks

- 1000 IU of CINRYZE every 3 or 4 days 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.

The safety and effectiveness of CINRYZE have not been established in children (see Clinical Trials, Pediatric population and Action and Clinical Pharmacology, Special Populations and Conditions).

3.3 Administration

Reconstitution and administration of CINRYZE

For intravenous use only.

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

Preparation and handling
CINRYZE is intended for intravenous administration after reconstitution with Sterile Water for Injections.

Each pack contains:
Two powder vials and two diluent vials.

Reconstitution, product administration and handling of the needles must be done with caution. A silicone-free syringe is recommended for reconstitution and administration of CINRYZE.

Use either a filter transfer device or any commercially available double-ended needle (see Dosage Forms, Strengths, Composition and Packaging).

3.4 Reconstitution

Table - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
8 mL	5 mL of Sterile Water for Injections	After reconstitution, one vial contains 500 IU of C1 inhibitor (human) in 5 mL	5 mL of C1 inhibitor corresponding to a concentration of 100 IU/mL

Each product vial should be reconstituted with 5 mL Sterile Water for Injections.

Two vials of reconstituted CINRYZE are combined for ONE dose (1000 IU).

1. Bring the powder vial and the diluent vial to room temperature (15ºC – 25ºC) prior to reconstitution.

2. Wash your hands before performing the following procedures.
3. Aseptic technique should be used during the reconstitution procedure.
4. Remove plastic caps from the powder and diluent 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. To maintain sterility, do not remove the device from the package.
7. Note: the transfer device must be attached to the diluent vial before being attached to the powder vial, so that the vacuum in the powder vial is not lost. Place the diluent vial on a flat surface and insert the blue end of the transfer device into the diluent vial, pushing down until the spike penetrates through the centre of the diluent 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 inadvertently remove the transfer device or touch the exposed end of the transfer device.
9. Place the powder vial on a flat surface. Invert the transfer device and the diluent vial containing Sterile 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 diluent. If there is no vacuum in the vial, do not use the product.
10. Gently swirl the powder vial until all powder is completely dissolved. Do not shake the powder vial.
11. Disconnect the diluent vial by turning it counter-clockwise. Do not remove the clear end of the transfer device from the powder vial.

ONE vial of reconstituted CINRYZE contains 500 IU of C1 inhibitor in 5 mL, resulting in a concentration of 100 IU/mL.

TWO vials of CINRYZE powder must be reconstituted to make one dose (1000 IU/10 mL). Therefore, repeat instructions 1 to 11 above using an additional transfer device to reconstitute the second of two powder vials. Do not reuse the transfer device. CINRYZE must be administered at room temperature within 3 hours after reconstitution.

Administration process

1. Aseptic technique should be used during the administration procedure.
2. After reconstitution, the CINRYZE solutions are colorless to slightly blue and clear. Do not use the product if the solutions are turbid or discolored.
3. Using a sterile, disposable 10 mL syringe, draw back the plunger to allow approximately 5 mL of air into the syringe. Use of a silicone-free syringe is recommended.
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 counter-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. CINRYZE should be administered promptly after preparation in the syringe and should not be used if particles are observed or if the solution is turbid.
8. Attach a needle to the syringe containing CINRYZE solution and inject intravenously into the patient. Administer 1000 IU (reconstituted in 10 mL of Sterile 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.

4 OVERDOSAGE

There has been no overdosage of CINRYZE reported during clinical studies. The maximum dose administered to HAE patients in clinical trials was 4000 Units given over approximately 4 hours (an average dose of 57 Units/kg) and 10,000 Units given over a 7 day period.

Thrombotic events have been reported in association with another C1 inhibitor product when used off label at high doses.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	Powder for solution, 500 IU/vial	L alanine, L-threonine, L-valine, sodium chloride, sodium citrate, sucrose

CINRYZE is supplied in a package containing 2 single-use vials with 500 IU of lyophilized human C1 inhibitor for reconstitution and 2 vials with 5 mL of Sterile Water for Injections (diluent).

Each vial of CINRYZE is for single use only and is supplied as 500 IU of C1 inhibitor in a colorless glass vial (Type I), sealed with a rubber stopper (Type I) and an aluminum seal with a plastic flip-off cap. Non-medicinal ingredients include L-alanine, L-threonine, L-valine, sodium chloride, sodium citrate and sucrose.

Sterile Water for Injections (5 mL) is needed for reconstitution. This is supplied in a colourless glass vial (Type I), closed with a rubber stopper (Type I) and an aluminum seal with a plastic flip-off cap.

6 DESCRIPTION

CINRYZE (C1 inhibitor [human]) is a sterile, stable, lyophilized preparation of C1 inhibitor derived from human plasma. CINRYZE is manufactured from large pools of human plasma purified by a combination of filtration and chromatographic procedures.

Following reconstitution with 5 mL of Sterile Water for Injections, each vial contains approximately 500 IU of functionally active C1 inhibitor. One IU of CINRYZE corresponds to the mean quantity of C1 inhibitor present in 1 mL of normal fresh plasma.

This product is prepared from large pools of human plasma which may contain the causative agents of hepatitis and other viral diseases.

7 WARNINGS AND PRECAUTIONS

General

Transmissible Agents

CINRYZE is made from human blood and it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens.

Home-treatment and 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.

Cardiovascular

***Thrombotic events*:**

Thrombotic events have been reported in patients receiving CINRYZE. Patients with known risk factors for thrombotic events should be monitored closely.

An animal study identified that there is a potential thrombogenic threshold at doses greater than 200 Units/kg.

In an open-label trial where 146 subjects received CINRYZE for prevention of HAE attacks, 5 serious thrombotic events (including myocardial infarction, deep vein thrombosis, pulmonary embolism and 2 events of cerebrovascular accident) occurred. None of these events were considered by the investigator to be related to CINRYZE.

Monitoring and Laboratory Tests

Monitor patients with known risk factors for thrombotic events.

Sensitivity/Resistance

Hypersensitivity:

Severe 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, urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis, which may occur during or after injection of CINRYZE. In case of hypersensitivity, discontinue CINRYZE infusion and initiate appropriate treatment.

7.1 Special Populations

7.1.1 Pregnant Women

It is not known whether CINRYZE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity (see NON-CLINICAL TOXICOLOGY). CINRYZE should be given to pregnant women only if clearly indicated.

7.1.2 Breast-feeding

It is unknown whether C1 inhibitor is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CINRYZE is administered to a nursing woman.

7.1.3 Pediatrics

The safety and effectiveness of CINRYZE have not been established in children (see Clinical Trials, Pediatric population and Action and Clinical Pharmacology, Special Populations and Conditions).

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 to prevent capillary leak syndrome.

7.1.4 Geriatrics

No special investigations have been performed.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical studies, there were a total of 262 subject exposures involving over 14,500 infusions of CINRYZE.

The most common adverse reaction observed following CINRYZE infusion in clinical studies was rash. Descriptions of rash characteristics were nonspecific, 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.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from

clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reaction frequency was estimated primarily based on summation of unique adverse events related to CINRYZE reported across 8 completed clinical studies in HAE subjects (Table 1). This includes data from two placebo-controlled studies, three open-label studies, and three compassionate-use single-subject studies. There were a total of 262 subject exposures involving over 14,500 infusions of CINRYZE in these studies.

The most common adverse reaction observed following CINRYZE infusion in clinical studies was rash.

Table 1. Adverse reactions with suspected relationship to CINRYZE reported in clinical studies by investigators

System Organ Class	Frequency*:	Adverse reaction
Metabolism and nutrition disorders	Uncommon:	Hyperglycemia
Nervous system disorders	Uncommon:	Dizziness, headache
Vascular disorders	Uncommon:	Hot flush, phlebitis, venous burning, venous thrombosis
Respiratory, thoracic and mediastinal disorders	Uncommon:	Cough
Gastrointestinal disorders	Uncommon:	Abdominal pain, diarrhea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Uncommon:	Rash Contact dermatitis, erythema, pruritus
Musculoskeletal and connective tissue disorders	Uncommon:	Arthralgia, joint swelling, myalgia
General disorders and administration site conditions	Uncommon:	Chest discomfort, infusion site pain, injection site rash/erythema, pyrexia

* Frequencies are defined as very common (≥10%), common (≥1% to <10%), uncommon (≥0.1% to <1%), rare (≥0.01% to <0.1%), and very rare (<0.01%).

8.3 Post-Market Adverse Reactions

Post-marketing thrombotic events have been reported, including catheter-related and deep venous thromboses, transient ischemic attack, and stroke. Patients with known risk factors for thrombotic events should be monitored closely (see **WARNINGS AND PRECAUTIONS**, **Thrombotic events**).

Other post-marketing adverse reactions reported include abdominal pain, anxiety, chest pain, diarrhea, dizziness, fatigue, headache, hypersensitivity, local infusion site reactions (including pain, rash, erythema, inflammation or hematoma at the infusion site), malaise, migraine, nausea, pain (of any type), rash, sinusitis, swelling (of any type), urticaria, and vomiting.

9 DRUG INTERACTIONS

9.1 Overview

No formal drug interaction studies have been conducted with CINRYZE, and to date no relevant interactions are known.

9.2 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted.

9.3 Drug-Food Interactions

No formal drug-food interaction studies have been conducted.

9.4 Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted.

9.5 Drug-Laboratory Test Interactions

No formal drug-laboratory interaction studies have been conducted.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

C1 inhibitor is a normal constituent of human blood and 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 human plasma which, in its mature state, consists of 478 amino acids with a molecular mass of 105 kilodaltons.

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 binding 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 inhibitor 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.

10.2 Pharmacodynamics

In a study of acute treatment of HAE, 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 and temporarily restores the natural regulation of the contact, complement, and fibrinolytic systems, thereby controlling swelling or the propensity to swell.

Pharmacodynamic Effects

Low C4 levels may be seen in patients with HAE attacks. Treatment with CINRYZE in 35 subjects showed the subsequent increase in plasma C4 levels, from an average of C4 8.1 mg/dL at baseline to C4 8.6 mg/dL, 12 hours after infusion of CINRYZE.

Complement C4 levels were also measured in a randomised, parallel-group, open-label pharmacokinetic study of CINRYZE in asymptomatic HAE subjects. 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.

At baseline, mean C4 complement levels were 6.5 ± 5.39 and 8.5 ± 6.28 mg/dL in the single-dose and double-dose groups, and increased to a maximum of 11.2 ± 6.2 and 16.5 ± 5.8 mg/dL, respectively. The time to maximum complement C4 concentrations was approximately 48 hours after the start of infusion, returning to near baseline levels at day 7.

10.3 Pharmacokinetics

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 Unit dose followed by a second dose of 1000 Units 60 minutes later.

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_{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.

Metabolism: 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 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.

Pharmacokinetics
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

Parameters	Single Dose (1000 Units*)	Double Dose (1000 Units dose followed by a second 1000 Units dose 60 minutes later)
$C_{baseline}$ (Units/mL)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C_{max} (Units/mL)	0.68 ± 0.08 (n = 12)	0.85 ± 0.12 (n = 13)
Baseline-corrected C_{max} (Units/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)
$AUC_{(0-t)}$ (Units*hr/mL)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
Baseline-corrected $AUC_{(0-t)}$ (Units*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_{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 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. No specific studies have been conducted to evaluate the pharmacokinetics of CINRYZE in patients with hepatic or renal impairment.

Special Populations and Conditions

Pediatrics: Functional C1 inhibitor activity was measured in children in the open-label study (see **CLINICAL TRIALS**). Mean increases from baseline in functional C1 inhibitor activity measured 1 hour post dose in children 3 to <18 years of age ranged from 22% to 46% in study LEVP 2006-4 compared with 25% to 32% in adults.

Geriatrics: No special investigations have been performed.

Hepatic Insufficiency: No specific studies have been conducted to evaluate the pharmacokinetics of CINRYZE in patients with hepatic impairment.

Renal Insufficiency: No specific studies have been conducted to evaluate the pharmacokinetics of CINRYZE in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Temperature

When stored between 2ºC–25ºC this product is stable in its original container. Do not freeze. Store in the original package in order to protect from light.

Keep in a safe place out of the reach of children.

The reconstituted solution must be used within 3 hours of reconstitution. After reconstitution, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (15℃–25℃).

Do not use beyond the kit expiration date.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: CINRYZE

Chemical name: C1 esterase inhibitor (human)

Molecular mass: approximately 105 kilodaltons (kDa)

Structural formula: C1 esterase inhibitor consists of 478 amino acids: an N-terminal domain of 113 amino acids and a serine-proteinase inhibitor or "serpin" domain of 365 amino acids.

Physicochemical properties: Soluble single-chain glycoprotein of which carbohydrate chains account for 26% to 35% of its weight.

Product Characteristics

CINRYZE (C1 esterase inhibitor [human]) is a sterile, stable, lyophilized preparation of C1 inhibitor derived from human plasma. CINRYZE is manufactured from human plasma purified by a combination of filtration and chromatographic procedures. The specific activity of CINRYZE is 4.0–9.0 IU/mg protein. Following reconstitution with 5 mL of Sterile Water for Injections, each vial contains approximately 500 IU of functionally active C1 inhibitor, pH 6.6–7.4, and an osmolality between 200–400 mOsmol/kg. One IU of CINRYZE corresponds to the mean quantity of C1 inhibitor present in 1 mL of normal fresh plasma.

CINRYZE, when reconstituted with 5 mL of Sterile Water for Injections, contains the following excipients: 4.1 mg/mL sodium chloride, 21 mg/mL sucrose, 2.6 mg/mL sodium citrate, 2.0 mg/mL L-Valine, 1.2 mg/mL L-Alanine, and 4.5 mg/mL L-Threonine.

Viral Inactivation

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.

CINRYZE is a highly purified, viral-inactivated, nanofiltered concentrate of human C1 inhibitor that was developed specifically to further minimize the risk of transmission of infectious agents over earlier generation C1 inhibitor products. The manufacturing process utilized to extract CINRYZE from human plasma incorporates three virus inactivation/removal steps: PEG precipitation, pasteurisation, and nanofiltration. These processes result in reduction of at least 16.7 $\log_{10}$ for the enveloped viruses tested (HIV, BVDV, PRV), at least 8.8 $\log_{10}$ for the non enveloped viruses (HAV, CPV), and >10 $\log_{10}$ reduction in prion-like material.

The measures taken are considered effective for enveloped viruses such as Human

Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), and for the non-enveloped viruses Hepatitis A Virus (HAV) and parvovirus B19. More than 14,000 doses of CINRYZE have been administered to over 260 different patients in all completed, controlled and open-label clinical studies. All patients who were evaluated were found negative for seroconversion to parvovirus B19, Hepatitis B, Hepatitis C and HIV.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Data from one randomized, double-blind, placebo-controlled study (LEVP 2005 1/B) and one open-label study (LEVP 2006 4) demonstrated the efficacy of CINRYZE for prevention of angioedema attacks in subjects with hereditary angioedema (HAE).

CINRYZE for the Routine Prevention of HAE Attacks

Table 3 - Summary of patient demographics for clinical trials of CINRYZE in prevention of HAE attacks

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
LEVP 2005-1/B	Randomized, double-blind, placebo-controlled, crossover	IV 1000 IU/Placebo (N=11) IV Placebo/1000 Units (N=11) Subjects were treated every 3 to 4 days for 12 weeks in both therapy periods	22	1000 Units/ Placebo: 40.0 (14-73) Placebo /1000 Units: 35.0 (9-64)	1000 Units/ Placebo: 2 M / 9 F Placebo/ 1000 Units: 0 M / 11 F
LEVP 2006-4	Open-label	IV 1000 Units Subjects were treated every 3 to 7 days for the study duration	146	36.0 (3-82)	34 M / 112 F

Study LEVP 2005-1/B used a randomized, double-blind, placebo-controlled, crossover design. Patients were screened to confirm a diagnosis of HAE and a history of at least two HAE attacks per month. 24 patients (mean age 38.5 years with a range of 9 to 73 years) were randomized to one of two treatment groups: either CINRYZE prophylaxis for 12 weeks followed by 12 weeks of placebo prophylaxis, or placebo prophylaxis for 12 weeks followed by 12 weeks of CINRYZE prophylaxis. The administration of open-label CINRYZE for treatment of HAE attacks in either period of the crossover was permitted. Two subjects dropped out (one in each arm); 22 patients

crossed over into period 2 and were included in the efficacy analysis.

Patients were given blinded injections (CINRYZE or placebo) every 3 to 4 days, approximately 2 times per week. Patients recorded all angioedema symptoms daily. An attack was defined as the subject-reported indication of swelling at any location following a report of no swelling on the previous day.

The efficacy determination was based on the number of attacks during the 12 week period while receiving CINRYZE as compared to the number of attacks during the placebo treatment period.

The effectiveness of CINRYZE prophylaxis in reducing the number of HAE attacks was variable among the subjects, as shown in Table 4.

14.2 Study Results

Table 4. Summary of Clinical Trial Results by Individual Subject: Efficacy Dataset (LEVP 2005-1/B)

Subject	Attacks on C1INH	C1INH Period Length (Days)	Attacks on Placebo	Placebo Period Length (Days)	Percent Reduction in Number of Attacks	Percent Reduction in Attack Frequency
1	0	81	6	85	100%	100.0%
2	0	34	7	96	100%	100.0%
3	0	81	14	82	100%	100.0%
4	0	83	14	80	100%	100.0%
5	2	84	22	96	91%	89.6%
6	1	82	9	86	89%	88.3%
7	2	81	13	83	85%	84.2%
8	2	81	12	85	83%	82.5%
9	2	81	9	81	78%	77.8%
10	2	85	8	82	75%	75.9%
11	8	81	20	82	60%	59.5%
12	10	85	19	86	47%	46.7%
13	7	82	14	93	50%	43.3%
14	7	82	10	67	30%	42.8%
15	11	81	17	85	35%	32.1%
16	13	81	19	82	32%	30.7%
17	6	80	8	80	25%	25.0%
18	12	82	15	81	20%	21.0%
19	12	82	14	86	14%	10.1%
20	6	85	6	84	0%	1.2%
21	17	81	16	82	-6%	-7.6%
22	15	86	8	85	-88%	-85.3%

Table 5. Summary of Clinical Trial Results by Prophylactic Therapy Period: Efficacy Dataset (LEVP 2005-1/B)

	Statistic	CINRYZE (N=22)	Placebo (N=22)

Number of Attacks	Mean ± SD	6.1 ± 5.4	12.7 ± 4.8
	Median (range)	6 (0 – 17)	13.5 (6 – 22)
GEE Analysis Results			
Effect Assessed		**p-value**	
Treatment Effect		<0.0001	
Sequence Effect		0.3347	
Period Effect		0.3494	

Table 6. Study LEVP 2005-1/B Secondary Endpoints: Efficacy Dataset

Efficacy Dataset	**CINRYZE (N=22)**	**Placebo (N=22)**	**95% CI for Treatment Effect (Placebo minus CINRYZE)**	**p-value [a]**
Severity of Attacks				
Mean ± SD	1.3 ± 0.85	1.9 ± 0.35	0.58	0.0008
Range	0 – 3 [b]	1 – 3	(0.19, 0.97)	
Duration of Attacks (days)				
Mean ± SD	2.1 ± 1.13	3.4 ± 1.39	1.23	0.0004
Range	0 – 4 [c]	2 – 8	(0.49, 1.96)	
Days of Swelling				
Mean ± SD	10.1 ± 10.73	29.6 ± 16.90	19.5	<0.0001
Range	0 – 38	8 – 67	(11.94, 27.06)	
Number of Open-label CINRYZE Infusions for Breakthrough Attacks				<0.0001
Mean ± SD	4.7 ± 8.66	15.4 ± 8.41	10.68	
Range	0 – 36	2 – 34	(7.09, 14.28)	

a: The significance level (alpha level) used for the secondary endpoints is 0.0125, based on a post-hoc adjustment for multiplicity using the Bonferroni method.

b: Average attack severity was set to 0 when there was no attack during a therapy period.

c: Average attack duration was set to 0 when there was no attack during a therapy period.

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). Subjects ranged in age from three to 82 years of age; 77% were female and 23% were male, and 83% were Caucasian. 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 ≤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.

At enrollment, 42 subjects (28.8%) were taking regular prophylactic androgens. During the study, 23 subjects (54.8%) discontinued androgens, 6 subjects (14.3%) discontinued regular use and switched to as-needed use, 5 subjects (11.9%) reduced the androgen dose, and 8 subjects (19.0%) remained on the same dose.

Nine (9) subjects not taking androgens at entry were prescribed androgens during their

participation in the study. Of these, 5 subjects were prescribed androgens for short-term prophylaxis and 4 subjects were started on regular androgens.

Pediatric population
Prevention (LEVP 2006-4): Prior to enrollment, 23 children (age range: 3-17) reported a median monthly HAE attack rate of 3.0 (range: 0.5-28.0). During the study while receiving prophylaxis using CINRYZE, children in the various age subgroups experienced a median monthly HAE attack rate 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.

In study 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.

15 NON-CLINICAL TOXICOLOGY

No animal studies have been completed to evaluate the effects of CINRYZE on carcinogenesis, mutagenesis, and impairment of fertility.

Toxicology studies up to 14 days duration in animals did not identify any treatment-related toxicity. Antibodies against the human protein were produced, however, the antibodies were not characterized for neutralizing activity and did not have any impact on C1 esterase activity.

An animal study showed that a potential thrombogenic threshold for CINRYZE was identified at the dose >200 Units/kg.

In an embryofetal development study (C1 inhibitor administered during the period of organogenesis) in rats, there was no maternal or fetal toxicity at doses up to 400 Units/kg that provided an exposure similar to that in humans after a 1000 Units dose.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

CINRYZE®*
C1 esterase inhibitor (human)

Read this carefully before you start taking **CINRYZE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CINRYZE.**

What is CINRYZE used for?
- Routine prevention of angioedema attacks in adults and adolescents with hereditary angioedema (HAE)

How does CINRYZE work?
Hereditary angioedema (HAE) is a hereditary disorder that is the most direct consequence of a lack of a functional naturally occurring blood protein called C1 inhibitor. C1 inhibitor deficiency in HAE patients can result in attacks of non-itching swellings of various regions of the body, including the hands and feet, face, intestines, genitals or the throat. Swelling of the throat can be life-threatening.

CINRYZE is a concentrate of C1 inhibitor. Clinical data has shown CINRYZE to treat and prevent the swelling associated with HAE by increasing the levels of functional C1 inhibitor in the body.

What are the ingredients in CINRYZE?
Medicinal ingredients: C1 inhibitor (human) is a concentrate of the naturally occurring C1 inhibitor found in human blood.
Non-medicinal ingredients: L alanine, L-threonine, L-valine, sodium chloride, sodium citrate, sucrose

CINRYZE comes in the following dosage forms:
CINRYZE is available in a single-use vial containing 500 IU of dried, pasteurized and lyophilized human C1 inhibitor concentrate to be reconstituted with 5 mL of Sterile Water for Injections prior to its intravenous administration. 1000 IU equals one dose of CINRYZE.

Do not use CINRYZE if:
- You have had life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 inhibitor products used to treat HAE or any of the CINRYZE ingredients or container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CINRYZE. Talk about any health conditions or problems you may have, including if you:
- Have a history of blood clotting problems. Very high doses of C1 inhibitor could increase the risk of blood clots.
- Are pregnant or planning to become pregnant. It is not known if CINRYZE can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if CINRYZE passes into your milk and

if it can harm your baby.
- Have any allergies to this drug or its ingredients or components of the container. Tell your doctor **immediately** if you experience allergic symptoms (sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching) after taking this medicine. Although they are rare, allergic symptoms can be severe.

CINRYZE is made from human blood and it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, and unknown or emerging viruses and other pathogens.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CINRYZE:
To date, no relevant interactions are known.

How to take CINRYZE:
See Usual dose below.

Usual dose:
Routine prevention of angioedema attacks
- 1000 IU of CINRYZE every 3 or 4 days for routine prevention against angioedema attacks.

CINRYZE is usually injected into a vein (intravenously) by your doctor or nurse. You or your caregiver may 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. Regular review of your/your caregiver's injection technique will be performed to ensure continued appropriate handling.

A patient/caregiver should not attempt to home- or self-administer unless trained by a healthcare provider.

Reconstitution and administration of CINRYZE
Reconstitution, product administration and handling of the needles must be done with caution. A silicone-free syringe is recommended for reconstitution and administration of CINRYZE.

Use either a filter transfer device or a commercially available double-ended needle.

Preparation and handling
CINRYZE is intended for intravenous administration after reconstitution with Sterile Water for Injections. Each vial of CINRYZE is for single use only.

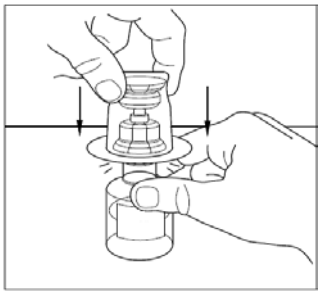
If you have any further questions regarding the use of this medicine, ask your doctor or pharmacist.

Reconstitution
Each product vial should be reconstituted with 5 ml Sterile Water for Injections. Two vials of reconstituted CINRYZE are combined for ONE dose (1000 IU).

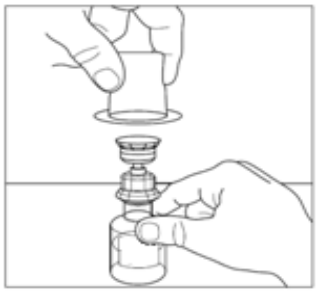
1. Bring the powder vial and the diluent vial to room temperature (15ºC–25ºC).

2. Wash your hands before performing the following procedures.
3. Aseptic technique should be used during the reconstitution procedure.
4. Remove plastic caps from the powder and diluent 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.

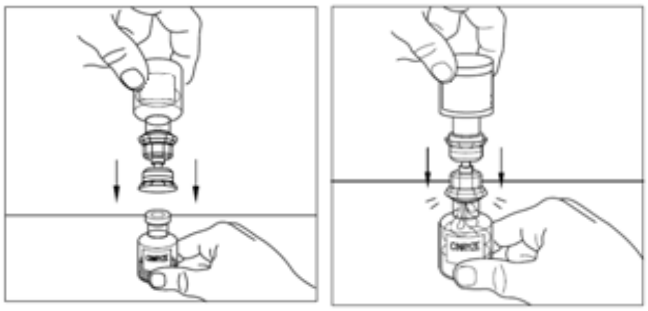
7. Note: the transfer device must be attached to the diluent vial before being attached to the powder vial, so that the vacuum in the powder vial is not lost. Place the diluent vial on a flat surface and insert the blue end of the transfer device into the diluent vial, pushing down until the spike penetrates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

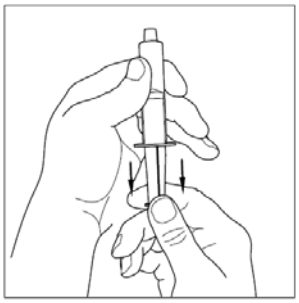
11. Disconnect the diluent vial by turning it counter-clockwise. Do not remove the clear end of the transfer device from the powder vial.

ONE vial of reconstituted CINRYZE contains 500 IU of C1 inhibitor in 5 mL, resulting in a concentration of 100 IU/mL.

TWO vials of CINRYZE powder must be reconstituted to make one dose (1000 IU/10 mL). Therefore repeat instructions 1 to 11 above using an additional transfer device to reconstitute the second of two powder vials. Do not reuse the transfer device. CINRYZE must be administered at room temperature within 3 hours after reconstitution.

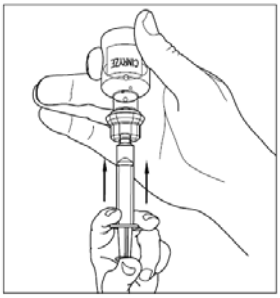
Administration process

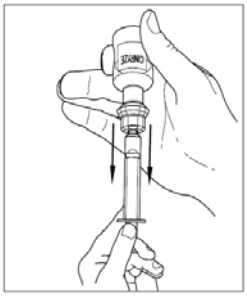
1. Aseptic technique should be used during the administration procedure.
2. After reconstitution, the CINRYZE solutions are colourless to slightly blue and clear. Do not use the product if the solutions are cloudy or discoloured.
3. Using a sterile, disposable 10 mL syringe, draw back the plunger to allow approximately 5 mL of air into the syringe. Use of a silicone-free syringe is recommended.



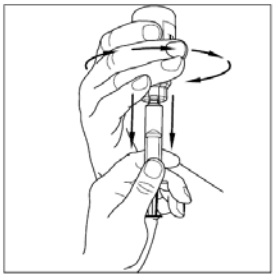
4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise.

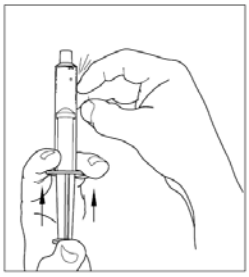
5. Invert the vial and inject air into the solution and then slowly withdraw the reconstituted CINRYZE solution into the syringe.





6. Detach the syringe from the vial by turning it counter-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. CINRYZE should be administered promptly after preparation in the syringe and should not be used if particles are observed or if the solution is cloudy.

8. Attach a needle to the syringe containing CINRYZE solution and inject intravenously into the patient. Administer 1000 IU (reconstituted in 10 mL of Sterile Water for Injections) of CINRYZE by intravenous injection at a rate of 1 mL per minute over 10 minutes.

Overdose:

If you think you have taken too much CINRYZE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Call your healthcare provider if you miss a dose of CINRYZE.

What are possible side effects from using CINRYZE?
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, allergic symptoms can be severe.

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

The most common side effect is rash.

Other side effects include: dizziness, headache, blood clot, painful veins, hot flush, nausea, vomiting, skin flaking, itching or redness, infusion site rash or pain, and fever.

These are not all the possible side effects you may feel when taking CINRYZE. If you experience any side effects not listed here, contact your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Do not use CINRYZE after the expiry date which is stated on the carton or vials after “EXP”. Store and transport between 2◦C 25◦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.

Keep out of reach and sight of children.

If you want more information about CINRYZE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.takeda.com/en-ca, or by calling Innomar Strategies, Inc. at 1-888-960-8746.

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