

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CINRYZE safely and effectively. See full prescribing information for CINRYZE.

CINRYZE [C1 Inhibitor (Human)]

For Intravenous Use, Freeze-Dried Powder for Reconstitution

Initial U.S. Approval: 2008

INDICATIONS AND USAGE

CINRYZE is a C1 inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

DOSAGE AND ADMINISTRATION

- Intravenous Use Only**
- Prior to reconstitution, protect from light.**
- Store at 2 °C - 25 °C (36 °F - 77 °F). Do not freeze.
- To obtain the required dose, reconstitute 2 CINRYZE vials with 2 vials Sterile Water for Injection, USP (5 mL each) using aseptic sterile technique.
- Administer at room temperature within 3 hours of reconstitution.

Routine Prophylaxis Dosing

Indication	Dose	Initial Infusion rate	Maintenance infusion rate (if tolerated)
Routine prophylaxis against HAE attacks	1,000 units Intravenous every 3 or 4 days	1 mL/min (10 min)	1 mL/min (10min)

DOSAGE FORMS AND STRENGTHS

Approximately 500 Units (lyophilized) in a 8 mL vial.

CONTRAINDICATIONS

Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product (4).

WARNINGS/PRECAUTIONS

- Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions (5.1).
- Thrombotic events have occurred in patients receiving off-label high dose C1 inhibitor therapy (5.2). Monitor patients with known risk factors for thrombotic events.
- CINRYZE is made from human plasma and may contain infectious agents e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent. (5.3)

ADVERSE REACTIONS

In the clinical trial, the most common adverse reactions observed by $\geq 5\%$ of subjects after CINRYZE treatment were upper respiratory tract infection, sinusitis, rash, and headache. (5.1, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lev Pharmaceuticals, Inc. at (877) 945-1000 or FDA at 1-800-FDA1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

CINRYZE™ C1 Inhibitor (Human) Freeze dried powder

1 INDICATIONS AND USAGE

CINRYZE is a C1 inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

2 DOSAGE AND ADMINISTRATION

For Intravenous Use, Freeze-Dried powder for Reconstitution.

2.1 Routine prophylaxis against HAE Attacks

- A dose of 1,000 Units CINRYZE can be administered every 3 or 4 days for routine prophylaxis against angioedema attacks in HAE patients.
- CINRYZE is administered at an injection rate of 1 mL per minute.

Table 2 **Routine Prophylaxis Dosing**

Indication	Dose (Total)	Initial Infusion rate	Maintenance infusion rate (if tolerated)
Routine prophylaxis against HAE attacks	1,000 units Intravenous every 3 or 4 days	1 mL/min (10 minutes)	1 mL/min (10 minutes)

2.2 Instructions for Use

The procedures below are provided as general guidelines for the reconstitution and administration of CINRYZE.

Always work on a clean surface and wash your hands before performing the following procedures.

Reconstitution, product administration, and handling of the administration set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted CINRYZE in an appropriate container.

2.3 Preparation and Handling

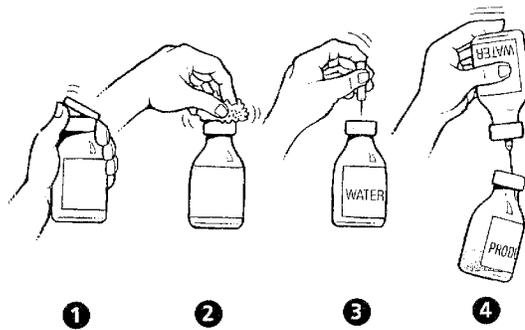
- **Prior to reconstitution, CINRYZE should be protected from light.**
- CINRYZE should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be colorless to slightly blue, and free from visible particles. Do not use if turbid or discolored.
- The CINRYZE vial is for single use only. CINRYZE contains no preservative. Any vial that has been entered should be used promptly. Partially used vials should be discarded in accordance with biohazard procedures.
- Do not mix CINRYZE with other materials.
- Do not freeze.
- Do not use after expiration date.

Reconstitution:

Two vials of reconstituted CINRYZE are combined for a single dose. Sterile Water for Injection, USP, is required and not supplied with CINRYZE.

1. Aseptic technique should be used during the reconstitution procedure.
2. Bring the CINRYZE (powder) and Sterile Water for Injection, USP (diluent) (not supplied) to room temperature if refrigerated.
3. Remove caps from the CINRYZE and diluent vials (Step 1).
4. Cleanse stoppers with germicidal solution, and allow them to dry prior to use. (Step 2)
5. Remove protective covering from one end of the double-ended transfer needle and insert exposed needle through the center of the diluent vial stopper (Step 3).
6. Remove protective covering from the other end of the double-ended transfer needle. Invert diluent vial containing 5 mL Sterile Water for Injection, USP, over the upright and slightly angled CINRYZE vial (Step 4); then rapidly insert the free end of the needle through the CINRYZE vial stopper at its center. The vacuum in the vial will draw in the diluent. **If there is no vacuum in the vial, do not use the product.**
7. Disconnect the two vials by removing the needle from the CINRYZE vial stopper and discard the diluent vial, along with the transfer needle directly into the sharps container. Gently swirl the CINRYZE vial until all powder is dissolved. Be sure that CINRYZE is completely dissolved.

One vial of reconstituted CINRYZE contains 5 mL of C1 inhibitor at a concentration of 100 Units/mL. Reconstitute two vials of CINRYZE for one dose.



2.4 Administration:

Two vials of reconstituted CINRYZE are combined for a single dose.

1. Use Aseptic Technique.
2. After reconstitution, the solution is colorless to slightly blue and clear. Do not use the product if the solution is turbid or discolored.
3. CINRYZE must be administered at room temperature within 3 hours after reconstitution.
4. Attach the filter needle to a sterile, disposable syringe and draw back the plunger to admit air into the syringe.
5. Insert the filter needle into the vial of reconstituted CINRYZE.
6. Inject air into the vial and then withdraw the reconstituted CINRYZE into the syringe. This should be repeated with a second vial of CINRYZE to make the complete dose.
7. Remove and discard the filter needle in a hard-walled Sharps container for proper disposal. Filter needles are intended to filter the contents of a single dose (2 vials) of CINRYZE only.
8. Attach a suitable needle or infusion set with winged adapter, and inject intravenously. As a guideline, administer 1,000 Units (reconstituted in 10ml) of CINRYZE by intravenous injection at a rate of 1 mL per minute over 10 minutes (*see Clinical Studies, Section 14*)
9. Dispose of all unused solution, the empty vial(s), and the used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.

3. DOSAGE FORMS AND STRENGTHS

- CINRYZE is a lyophilized preparation available in a single-use vial that contains 500 Units (U) human C1 inhibitor.
- Each vial must be reconstituted with 5 mL Sterile Water for Injection, USP (diluent) (not supplied)
- Two reconstituted vials must be used to make a single, 1,000 Units, dose.

4 CONTRAINDICATIONS

CINRYZE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Sensitivity

Severe hypersensitivity reactions may occur. The signs and symptoms of hypersensitivity reactions may include the appearance of hives, urticaria, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of CINRYZE.

Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered.

In case of hypersensitivity, CINRYZE infusion should be discontinued and appropriate treatment instituted. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction. (*See Patient Counseling Information [17]*)

5.2 Thrombotic Events

Thrombotic events have been reported in association with C1 Inhibitor products when used off-label at high doses.⁷ Animal studies have supported a concern about the risk of thrombosis from intravenous administration of C1 Inhibitor products.⁸ (*see Sections 10 OVERDOSAGE and 13.2 Animal Toxicology and/or Pharmacology*)

5.3 General

Because CINRYZE is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent [5.3, 11]. ALL infections thought by a physician possibly to have been transmitted by CINRYZE should be reported by the physician or other healthcare provider to Lev Pharmaceuticals, Inc [(877) 945-1000]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient (*See Patient Counseling Information [17]*).

6 ADVERSE REACTIONS

6.1 Adverse Reaction Overview

The most serious adverse events observed in clinical studies of CINRYZE have been death due to non-catheter related foreign body embolus, pre-eclampsia resulting in emergency C-section, stroke, and exacerbation of HAE attacks, none of which have been considered drug related.

The most common drug related adverse reactions observed at a rate $\geq 5\%$ were upper respiratory tract infections, sinusitis, rash, and headache.

6.2 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Routine Prophylaxis

Twenty-four subjects were evaluated in study LEVP2005-1/B for routine prophylaxis.

There were no treatment-emergent serious adverse reactions in study LEVP2005-1/B.

Adverse reactions in trial LEVP2005-1/B that occurred in at least two subjects during CINRYZE prophylaxis, irrespective of the causality assessment, are given in the following table:

Table 2
Adverse Reactions in Routine Prophylaxis Study LEVP1005-1/B
Irrespective of Causality

Adverse Reaction	Number of Adverse Events	Number of Subjects (N = 24)
Sinusitis	8	5
Rash	7	5
Headache	4	4
Upper respiratory tract infection	3	3
Viral upper respiratory tract infection	5	3
Bronchitis	2	2
Limb injury	2	2
Back pain	2	2
Pain in extremity	2	2
Pruritus	2	2

More than 9000 doses of CINRYZE have been administered to over 180 patients in all controlled and open label clinical studies. All patients were evaluated and found negative for seroconversion to parvovirus B19, Hepatitis B, Hepatitis C and HIV.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. No animal data are available. No adequate and well-controlled studies were conducted in pregnant women. It is not known whether CINRYZE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CINRYZE should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

The safety and effectiveness of CINRYZE administration prior to or during labor and delivery have not been established. Use only if clearly needed.

8.3 Nursing Mothers

It is not known whether CINRYZE 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.

8.4 Pediatric Use

The safety and effectiveness of CINRYZE have not been established in neonates, infants, or children. Three of the 24 subjects in Study LEVP2005-1/B were under the age of 18 years (9, 14, and 16 years of age).

8.5 Geriatric Use

The clinical study LEVP2005-1/B did not include sufficient numbers of subject 65 years of age and older to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

The maximum dose administered in clinical studies was 4000 Units given over approximately 5 hours (an average of 57 Units/kg) and 9000 Units given over a 7 day period. There have been no overdoses of CINRYZE reported during clinical studies.

In vitro and in vivo animal thrombogenicity studies with CINRYZE showed a potential for clot formation when CINRYZE was administered at doses 14 times the recommended clinical dose (greater than 200U/kg).. Thrombotic events have been reported in association with C1 Inhibitor products when used off-label at high doses.⁷ Animal studies have supported a concern about the risk of thrombosis from intravenous administration of C1 Inhibitor products.⁸ (*see Section 13.2 Animal Toxicology and/or Pharmacology and Section 5.2 Thrombotic events in WARNINGS AND PRECAUTIONS*).

11 DESCRIPTION

CINRYZE [C1 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 units/mg protein. The purity is $\geq 90\%$ human C1 inhibitor. Following reconstitution with 5 mL of Sterile Water for Injection, USP, each vial contains approximately 500 units of functionally active C1 inhibitor, pH 6.6 - 7.4, and an osmolality between 200 – 400 mosmol/kg. One unit (U) 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 Injection contains the following excipients: 4.1 mg/ml sodium chloride, 21 mg/ml sucrose, 2.6 mg/ml trisodium citrate, 2.0 mg/ml L-Valine, 1.2 mg/ml L-Alanine, and 4.5 mg/ml L-Threonine.

The following manufacturing steps are designed to reduce the risk of viral transmission:

- Screening donors at U.S. licensed blood collection centers to rule out infection with Human Immunodeficiency Virus (HIV-1/HIV-2), Hepatitis B Virus, or Hepatitis C Virus.
- Testing plasma pools by in-process NAT for parvovirus B19 (B19) via minipool testing and the limit of B19 in the manufacturing pool is set not to exceed 104 IU of B19 DNA per mL.
- Use of two independent viral reduction steps in the manufacture of CINRYZE: pasteurization (heat treatment at 60°C for 10 hours in solution with stabilizers) and nanofiltration through two sequential 15 nm Planova filters.

These viral reduction steps, along with a step in the manufacturing process, PEG precipitation, have been validated in a series of *in vitro* experiments for their capacity to inactivate/remove a wide range of viruses of diverse physicochemical characteristics including: Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), and the following model viruses: Bovine Viral Diarrhea Virus (BVDV) as a model virus for HCV, Canine Parvovirus (CPV) as a model virus for Parvovirus B19, Pseudorabies Virus (PRV) as a model virus for large enveloped DNA viruses (e.g. herpes virus). Total mean \log_{10} reductions are shown in Table 3.

Table 3 **Log₁₀ Reduction Factor for Selected Viruses**

Process step	Log ₁₀ Virus Reduction				
	Enveloped viruses			Non-enveloped viruses	
	HIV	BVDV	PRV	HAV	CPV
PEG precipitation	5.1 ± 0.2	4.5 ± 0.3	6.0 ± 0.3	2.8 ± 0.2	4.2 ± 0.2
Pasteurization	> 6.1 ± 0.2	> 6.7 ± 0.3	> 6.7 ± 0.2	2.8 ± 0.3	0.1 ± 0.3
Nanofiltration	> 5.6 ± 0.2	> 5.5 ± 0.2	> 6.4 ± 0.3	> 4.9 ± 0.2	> 4.5 ± 0.3
Total reduction	> 16.8	> 16.7	> 19.1	> 10.5	> 8.7

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

C1 inhibitor is a normal constituent of human blood and is one of the serine proteinase inhibitors (serpins). The primary function of C1 inhibitor is to regulate the activation of the complement and intrinsic coagulation (contact system) pathway. C1 inhibitor also regulates the fibrinolytic system. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1 inhibitor.

HAE patients have low levels of endogenous or functional C1 inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it is thought by some that increased vascular permeability and the clinical manifestation of HAE attacks are primarily mediated through contact system activation. Suppression of contact system activation by C1 inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin⁶. Administration of CINRYZE increases plasma levels of C1 inhibitor activity.

12.2 Pharmacodynamics

In clinical studies, the intravenous administration of CINRYZE demonstrated an increase in plasma levels of C1 inhibitor within approximately one hour or less of administration.

Biological activity of CINRYZE was shown in 35 subjects by the subsequent increase in plasma C4 levels from an average of C4 8.1 mg/mL at baseline to C4 8.6 mg/mL 12 hours after infusion of CINRYZE.

12.3 Pharmacokinetics

A randomized, parallel group, open label pharmacokinetics (PK) study of CINRYZE was performed in patients with non-symptomatic hereditary angioedema (HAE). The patients received either a single dose of 1,000 units or 1,000 units followed by a second 1,000 units 60 minutes later. The PK results for functional C1 inhibitor are presented the following table:

Table 4 **Mean pharmacokinetic parameters of Functional C1 Inhibitor**

Parameters	Single Dose	Double Dose
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)
T _{max} (hrs)	3.9 ± 7.3 (n = 12)	2.7 ± 1.9 (n = 13)
AUC _(0-t) (units*hr/mL)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
CL (mL/min)	0.85 ± 1.07 (n = 7)	1.17 ± 0.78 (n = 9)
Half-life (hours)	56 ± 36 (n = 7)	62 ± 38 (n = 9)

Numbers in parenthesis are number of subjects evaluated

One unit is equal to the mean C1 inhibitor concentration of 1 mL of normal human plasma
Single dose = 1,000 units
Double dose = 1,000 units followed by a second 1,000 units 60 minutes later

The maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased from the single to double dose, although the increase was not dose proportional. The mean half-lives of CINRYZE were 56 hours (range 11 to 108 hours) for a single dose and 62 hours (range 16 to 152 hours) for the double dose.

Studies have not been conducted to evaluate the PK of CINRYZE in special patient populations identified by gender, race, age (pediatric or geriatric), or the presence of renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

Acute toxicity of CINRYZE was studied in a combined acute toxicity and 7-day repeat dose/ dose range finding (DRF) study in Sprague Dawley rats. Repeat dose toxicity was studied in a 7-day repeat dose follow up to the acute dose study. The acute and repeated dose toxicity study were performed with intravenous administration of CINRYZE at dose levels of 1, 7 and 28 times normal dose. No signs of toxicity were observed in the single dose study. In the repeated dose study, no signs of toxicity were observed in the two lower doses. Repeat dosing in the rat resulted in a robust neutralizing antibody response between days 1 and 14. Therefore, toxicity in animals dosed repeatedly is difficult to interpret.

In vitro and in vivo thrombogenicity studies showed a potential for clot formation when CINRYZE was administered at doses 14 times the recommended clinical dose (greater than 200U/kg).

14 CLINICAL STUDIES

14.1 Routine Prophylaxis Trial LEVP2005-1/B

The safety and efficacy of CINRYZE prophylaxis therapy to reduce the incidence, severity, and duration of HAE attacks was demonstrated in a single randomized, double blind, placebo controlled multi-center cross-over study of 24 patients. Patients were screened to confirm a diagnosis of HAE and a history of at least two HAE attacks per month. 24 patients (mean age 38.1 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 randomized to placebo prophylaxis for 12 weeks followed by 12 weeks of CINRYZE prophylaxis. 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 C1 inhibitor prophylaxis in reducing the number of HAE attacks was variable among the subjects as shown in table 5:

Table 5
LEVP2005-1/B Prevention of HAE Attacks
Clinical Trial Results by Subject

Subject	Percent Reduction in Attack Frequency
1	100%
2	100%
3	100%
4	100%
5	90%
6	88%
7	84%
8	83%
9	78%
10	76%
11	60%
12	47%
13	43%
14	43%
15	32%
16	31%
17	25%
18	21%
19	10%
20	1%
21	-8%
22	-85%

Table 6 Summary Statistics on Number of HAE Attacks in LEVP2005-1/B

	Statistic	CINRYZE N=22	Placebo N=22
Number of Attacks	Mean	6.1	12.7
	SD	5.4	4.8
	Median	6	13.5
	Min	0	6
	Max	17	22
GEE Analysis Results			
Effect Assessed		p-value	
Treatment Effect		<0.0001	
Sequence Effect		0.3347	

Period Effect	0.3494
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Patients treated with CINRYZE had a 66% reduction in days of swelling ($p < 0.0001$), and decreases in the average severity of attacks ($p = 0.0006$) and the average duration of attacks ($p = 0.0023$), as shown in table 7.

Table 7 LEVP2005-1/B Clinical Trial Secondary Efficacy Outcomes

	CINRYZE N=22	Placebo N=22	Treatment Effect p-value
Mean Severity of HAE Attacks (Score from 1 to 3) (SD)	1.3(0.85)	1.9 (0.36)	0.0006
Mean Duration of HAE Attacks (Days) (SD)	2.1 (1.13)	3.4 (1.4)	0.0023
Days of Swelling (SD)	10.1 (10.73)	29.6 (16.9)	<0.0001

15 REFERENCES

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7. Arzneimittelkommission der Deutschen Aertzeschaft. Schwerwiegende Thrombenbildung nach Berinert HS. *Dtsch Aerztebl*. 2000; 97:B-864
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16 HOW SUPPLIED/STORAGE AND HANDLING

- CINRYZE is available in single-use vials that contain 500 Units per vial.
- CINRYZE is supplied as a single glass vial of CINRYZE powder to be reconstituted with 5 mL Sterile Water for Injection, USP (Not supplied).
- CINRYZE, packaged for sale, is stable for 1 year when stored at 2°C–25°C (36°F–77°F).
- Do not freeze.
- Store the vial in the original carton to protect it from light.
- The reconstituted solution must be used within 3 hours of reconstitution.
- Do not use beyond the expiration date on the CINRYZE vial.

17 PATIENT COUNSELING INFORMATION

(See *Warnings and Precautions Sections*)

- Prior to treatment, patients should fully understand the risks and benefits of CINRYZE.
- Inform patients to immediately report the following to their physician:

- signs and symptoms of allergic hypersensitivity reactions, such as hives, urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis experienced during or after injection of CINRYZE.
- signs and symptoms of thrombosis, such as new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness or speech.
- Inform patients that CINRYZE is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses, and, theoretically, the CJD agent). Inform patients that the risk CINRYZE may transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing the donated plasma for certain virus infections and by inactivating and/or removing certain viruses during manufacturing.
- Inform patients and their caregivers of the following:
 - **Prior to reconstitution, CINRYZE should be protected from light.**
 - Two 500 Unit vials are need to make a complete dose.
 - Reconstitute each vial of the lyophilized CINRYZE powder with 5 mL of the appropriate diluent (Sterile Water for Injection, USP) (not supplied) using a sterile transfer needle according to the directions in the package insert.
 - Gently swirl the vial until all powder is dissolved.
 - Visually inspect the solution for discoloration and particulate matter. The reconstituted solution should be colorless to slightly blue and free from visible particles. CINRYZE should not be administered if discoloration or particulate matter is observed. Do not use if turbid.
 - The solution is drawn through the sterile filter needle into a sterile disposable syringe.
 - The reconstituted solution contains no preservatives and is intended for single use only. Once reconstituted, the product must be administered by intravenous injection within 3 hours. All unused solution, empty vials and used needles must be discarded appropriately.

Manufactured by: Sanquin Blood Supply Foundation
Amsterdam, The Netherlands

Distributed by: Lev Pharmaceuticals, Inc.
New York, NY 10017
U.S. License Number 1780