CINRYZE™ PRODUCT INFORMATION

NAME OF MEDICINE

CINRYZE™, C1 Esterase Inhibitor (Human)

DESCRIPTION

CINRYZE as a single-use powder vial contains 500 Units of C1 esterase inhibitor (human) purified from the plasma of human donors. One Unit is equivalent to the mean quantity of C1 esterase inhibitor present in 1 ml of normal human plasma. After reconstitution, a single dose is 1000 Units/10 ml with a concentration of 100 Units/ml.

CINRYZE, as a white powder, contains the following excipients.
Sodium chloride (21 mg)
Sucrose (103 mg)
Sodium citrate (13 mg)
Valine (10 mg)
Alanine (6 mg)
Threonine (23 mg)

PHARMACOLOGY

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

Mechanism of action

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

C1 esterase inhibitor inhibits the complement system by binding C1r and C1s, two of the active enzyme subunits of the first component of the complement system (C1) in the classical pathway, as well as to mannose-binding lectin-associated serine proteases in the lectin pathway. The primary substrate of the activated C1 enzyme is C4; uninhibited C1 results in diminished C4 levels. C1 is the most important inhibitor of contact activation and regulates the contact system and the intrinsic coagulation pathway by binding to and inactivating kallikrein and factor XIIa. Because these pathways are part of enzyme amplification cascades, without C1 esterase inhibitor, spontaneous or trigger-induced activation of these pathways can lead to unopposed activation and swelling.

Pharmacodynamic effects

In a study of acute treatment of hereditary angioedema (HAE), intravenous administration of CINRYZE resulted in a significant increase in systemic levels of antigenic and functional C1 esterase inhibitor within 1 hour after administration. Administration of C1 esterase inhibitor increases serum levels of C1 esterase inhibitor activity and temporarily restores the natural regulation of the contact, complement, and fibrinolytic systems thereby controlling the swelling or the propensity to swell.

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

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.

Pharmacokinetics

In the open label study described above, the mean pharmacokinetic parameters for functional C1 esterase inhibitor derived from baseline-corrected concentration data are presented in Table 1.

Table 1. Mean pharmacokinetic parameters for functional C1 esterase 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)
$C_{baseline}$ (U/ml)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C_{max} (U/ml)	0.68 ± 0.08 (n = 12)	0.85 ± 0.12 (n = 13)
Baseline-corrected C_{max} (U/ml)	0.37 ± 0.15 (n=12)	0.51 ± 0.19 (n=12)
t_{max} (hr) [median (range)]	[1.2 (0.3 – 26.0)] (n = 12)	[2.2 (1.0 – 7.5)] (n = 13)
$AUC_{(0-t)}$ (U*hr/ml)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
Baseline-corrected $AUC_{(0-t)}$ (U*hr/ml)	24.5 ± 19.1 (n=12)	39.1 ± 20.0 (n=12)
CL (ml/min)	0.85 ± 1.07 (n = 7)	1.17 ± 0.78 (n = 9)
Elimination half-life (hr)	56 ± 35 (n = 7)	62 ± 38 (n = 9)

n= number of subjects evaluated.

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

Because C1 esterase inhibitor is an endogenous human plasma protein, it is not subject to metabolism by Cytochrome P450 iso-enzymes, excretion, or pharmacokinetic drug-drug interactions exhibited by many low molecular weight compounds. The expected consequence of metabolism of a glycoprotein is via degradation to small peptides and individual amino acids. As such, the pharmacokinetics and excretion of CINRYZE are not expected to be altered by renal or hepatic impairment.

Paediatric population

Functional C1 esterase inhibitor activity was measured in children in the two open label studies (see Clinical Trials section, below). Mean increases from baseline in functional C1 esterase inhibitor activity measured 1 hour post-dose in children 2 to <18 years of age ranged from 20% to 88% in Study LEVP 2006-1

(treatment) and from 22% to 46% in Study LEVP 2006-4 (prevention) compared with 21% to 66% and 25% to 32% in adults, respectively.

CLINICAL TRIALS

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 hereditary angioedema.

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 population consisted of subjects with a history of relatively frequent angioedema attacks (at least 2 per month on average) while on their current therapeutic regimen for HAE or no regimen at all. 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. 12.8attacks 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 ≤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 ≤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 esterase inhibitor levels post-infusion compared to pre-infusion values, with similar trends observed in children and adults.

INDICATIONS

Treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with C1 inhibitor deficiency.

Routine prevention of angioedema attacks in adults and adolescents with frequent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral therapy.

CONTRAINDICATIONS

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

PRECAUTIONS

General

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.

Thrombotic events

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

Paediatric population

Thrombotic events have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving high doses of another C1 INH 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.

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 (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.

The manufacturing process utilized to extract CINRYZE from screened human plasma incorporates three virus inactivation/removal steps: polyethylene glycol (PEG) precipitation (20% PEG 4000, pH 5.8), pasteurisation (10 hours at 60.5 ± 1.0 ºC) and 15 nm filtration to remove the smallest known viral particles (a process not utilized by all other currently available C1 esterase inhibitor products). Collectively, these processes result in reduction of at least 16.7 $\log_{10}$ for the enveloped viruses tested (HIV, Bovine Viral Diarrhea Virus (BVDV), Pseudorabies Virus (PRV)), at least 8.8 $\log_{10}$ for the non-enveloped viruses (HAV, Canine Parvovirus (CPV)), and >10 $\log_{10}$ reduction in prion-like material. Thus, while the infection-related risk associated with any plasma-derived product will never be zero, the manufacturing process for CINRYZE provides substantial protection against infections of C1 esterase inhibitor products to date and represents an important improvement in product safety.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived C1 esterase 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.

Sodium

Each vial of CINRYZE contains approximately 11.5 mg of sodium. To be taken into account by patients on a controlled sodium diet.

Effects on fertility

No studies on fertility or early embryonic and postnatal development were conducted because chronic dosing in animals would be expected to be associated with development of neutralising antibodies to the human protein.

Effects in pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of CINRYZE in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. The use of CINRYZE may be considered during pregnancy, if necessary.

Use in lactation

It is unknown whether C1 esterase inhibitor is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from CINRYZE therapy

taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Paediatric use

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

Use in elderly

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.

Carcinogenicity

No carcinogenicity studies were conducted because chronic dosing in animals would be expected to be associated with development of neutralising antibodies to the human protein.

Genotoxicity

No genotoxicity studies were performed as the drug is unlikely to interact directly with DNA or other chromosomal material.

INTERACTION WITH OTHER MEDICINES

No interaction studies have been conducted.

ADVERSE EFFECTS

Summary

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 study drug.

Local reactions at the injection site were uncommon. In clinical studies involving over 14,500 infusions of CINRYZE, 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.

Tabulated summary of adverse reactions

A summary of adverse reactions (i.e., those events with suspected relationship to treatment with CINRYZE based on the sponsor's overall assessment) CINRYZE are classified by System Organ Class and absolute frequency in Table 2. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000).

Table 2. Adverse Reactions Associated with the administration of CINRYZE

System Organ Class	Frequency: Adverse drug reaction
Nervous system disorders	Uncommon: Dizziness, headache
Vascular disorders	Uncommon: Venous thrombosis, phlebitis, venous burning, hot flush
Gastrointestinal disorders	Uncommon: Nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Rash Uncommon: Erythema, pruritus
General disorders and administration site conditions	Uncommon: Infusion site reactions, pyrexia

Paediatric data

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 study drug. Overall, the safety and tolerability of CINRYZE are similar in children and adults.

DOSAGE AND ADMINISTRATION

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

Dosage

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 should be administered if the patient has not responded adequately after 60 minutes.
- A second dose of 1000 Units is more likely to be required in patients experiencing severe attacks, laryngeal attacks or if initiation of treatment is delayed.

Routine prevention of angioedema attacks

- 1000 Units 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.

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 adolescent patients, the dose is the same as for adults.

There are limited data on the safety and efficacy of CINRYZE in children before adolescence and no dosing recommendation 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.

It is recommended that the product is injected intravenously at a rate of 1 ml per minute.

Each powder vial is reconstituted with 5 ml of water for injections and the two vials of reconstituted CINRYZE are combined for a single dose.

It is the responsibility of the prescribing physician to determine which patients may be suitable for self-administration of CINRYZE and to provide training. 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. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and handling

CINRYZE is intended for intravenous administration after reconstitution with water for injections.

CINRYZE vial is for single use in one patient only. Any vial that has been entered should be used promptly.

Reconstitution

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

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

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, if refrigerated.
4. Release the powder vial label by tearing down the perforated strip indicated by the inverted triangle.
5. Remove plastic caps from the powder and solvent vials.
6. Cleanse stoppers with an alcohol swab and allow them to dry prior to use.
7. Remove protective covering from the top of the transfer device package. Do not remove the device from the package.
8. Note: the transfer device must be attached to the solvent vial before being attached to the powder vial, so that the vacuum in the powder vial is not lost. Place the solvent vial on a flat surface and insert the blue end of the transfer device into the solvent vial, pushing down until the spike penetrates through the centre of the solvent vial stopper and the device snaps in place. The transfer device must be vertical prior to penetrating the stopper closure.
9. Remove the plastic package from the transfer device and discard it. Take care not to touch the exposed end of the transfer device.
10. Place the powder vial on a flat surface. Invert the transfer device and the solvent vial containing water for injections and insert the clear end of the transfer device into the powder vial, pushing down until the spike penetrates the rubber stopper and the transfer device snaps into place. The transfer device must be vertical

prior to penetrating the stopper closure of the powder vial. The vacuum in the powder vial will draw in the solvent. If there is no vacuum in the vial, do not use the product.

11. Gently swirl the powder vial until all powder is dissolved. Do not shake the powder vial. Make sure all the powder is completely dissolved.
12. Disconnect the solvent vial by turning it anti-clockwise. Do not remove the clear end of the transfer device from the powder vial.

ONE vial of reconstituted CINRYZE contains 500 Units of C1 esterase 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 12 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 gently and inject air into the solution and then slowly withdraw the reconstituted CINRYZE solution into the syringe.
6. Detach the syringe from the vial by turning it anti-clockwise and releasing it from the clear end of the transfer device.
7. Using the same syringe, repeat steps 3 to 6 with a second vial of reconstituted CINRYZE to make one complete 10 ml dose.
8. Inspect the reconstituted Cinryze solution for particulate matter prior to administration; do not use if particles are observed.
9. Attach the venipuncture set to the syringe containing CINRYZE solution and inject intravenously into the patient. Administer 1000 Units (reconstituted in 10 ml) of CINRYZE by intravenous injection at a rate of 1 ml per minute over 10 minutes.
10. Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

There have been no overdosages 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 esterase inhibitor product when used off label at high doses.

PRESENTATION AND STORAGE CONDITIONS

Presentation

CINRYZE Powder: CINRYZE is supplied in a single-use vial of colourless glass Type I, containing 500 Units of C1 esterase inhibitor as a nanofiltered, freeze-dried powder. The vial is sealed with a rubber Type I stopper, and an aluminium seal with a plastic flip-off cap.
Solvent: 5 ml of water for injections in a vial of colourless glass Type I, which is closed with a rubber Type I stopper 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 alcohol swabs, 1 protective mat.

Use of a silicone-free syringe is recommended for reconstitution and administration of the product. For your convenience, a silicone-free syringe is provided in the Administration set.

Storage Conditions

CINRYZE powder has a shelf life of two (2) years when stored below 25°C (room temperature).

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

Do not mix CINRYZE with other materials.

Do not use after expiration date (Exp).

Prior to reconstitution the product is a white powder. The product is for single use in one patient only. From a microbiological point of view, after reconstitution the product should be used immediately. If immediate use is not possible, the reconstituted product may be stored at 15 to 25 °C for not more than 3 hours.

NAME AND ADDRESS OF THE SPONSOR

ViroPharma Pty Ltd
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POISON SCHEDULE OF THE MEDCINE

CINRYZE is exempt from scheduling.

DATE OF FIRST ARTG INCLUSION

05/04/2012

DATE OF MOST RECENT AMENDMENT

15/04/2013

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