PACKAGE LEAFLET: INFORMATION FOR THE USER

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

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

What is in this leaflet:

1. What Cinryze is and what it is used for

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

C1 inhibitor is a naturally occurring protein that is normally present in the blood. If you have a low amount of C1 inhibitor in your blood or your C1 inhibitor is not working properly, this can lead to swelling attacks (called angioedema). Symptoms may include stomach pains and swelling of the:
- hands and feet
- face, eyelids, lips or tongue
- voice-box (larynx), which may make breathing difficult
- genitals

In adults and children, Cinryze can raise the amount of C1 inhibitor in the blood and either prevent (prior to undergoing medical or dental procedures) these swelling attacks from occurring or stop swelling attacks once they have begun.
In adults, adolescents and children (aged 6 years and above), Cinryze can raise the amount of C1 inhibitor in the blood and routinely prevent swelling attacks from occurring.

2. What you need to know before you take Cinryze

Do not take Cinryze
- If you are allergic to C1 inhibitor or any of the other ingredients of Cinryze (listed in section 6). It is important to tell your doctor if you think you have ever had an allergic reaction to any of the ingredients in Cinryze.

Warnings and precautions

- Before you start treatment with Cinryze, it is important that you tell your doctor if you have, or have had, problems with your blood clotting (thrombotic events). You will be carefully monitored if this is the case.
- If you begin to suffer from rashes, tightness of the chest, wheezing, or a fast heart beat once you have taken Cinryze, you should tell your doctor **immediately** (see section 4).
- When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

  The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B and hepatitis C viruses, and for the non-enveloped hepatitis A and parvovirus B19 viruses.

  Your doctor may recommend that you consider having vaccinations against hepatitis A and B if you regularly or repeatedly receive C1 inhibitor products that have been taken from human plasma.

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

Children

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

Other medicines and Cinryze

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

Pregnancy and breast-feeding

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

Driving and using machines

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

Cinryze contains sodium

Each vial of Cinryze contains approximately 11.5 mg of sodium. This should be taken into account by people on a controlled sodium diet.

3. How to take Cinryze

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

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

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

Adults and adolescents (12 years and above)

Treatment of swelling attacks
- A dose of 1000 IU (two vials) of Cinryze should be injected at the first sign of a swelling attack.
- A second injection of 1000 IU may be given if your symptoms do not improve after 60 minutes.
- If you are experiencing a severe attack, particularly a swelling of the voice-box (larynx), or if initiation of treatment is delayed, the second 1000 IU dose may be given earlier than 60 minutes after the first dose, depending on your clinical response.
- Cinryze should be injected intravenously (into the vein).

Routine prevention of swelling attacks
- A dose of 1000 IU (two vials) of Cinryze should be injected every 3 or 4 days for routine prevention of swelling attacks.
- The dosing interval may be adjusted by your doctor depending upon your response to Cinryze.
- Cinryze should be injected intravenously (into the vein).

Prevention of swelling attacks prior to surgery
- A dose of 1000 IU (two vials) of Cinryze should be injected up to 24 hours before a medical, dental, or surgical procedure.
- Cinryze should be injected intravenously (into the vein).

Children

Treatment of angioedema attacks	Pre-procedure prevention of angioedema attacks	Routine prevention of angioedema attacks
2 to 11 years, >25 kg: A dose of 1000 IU (two vials) of Cinryze should be injected at the first sign of a swelling attack. A second injection of 1000 IU may be given if your symptoms do not improve after 60 minutes. *2 to 11 years, 10-25 kg:* A dose of 500 IU (one vial) of Cinryze should be injected at the first sign of a swelling attack. A second injection of 500 IU may be given if your symptoms do not improve after 60 minutes.	*2 to 11 years, >25 kg:* A dose of 1000 IU (two vials) of Cinryze should be injected up to 24 hours before a medical, dental, or surgical procedure. *2 to 11 years, 10-25 kg:* A dose of 500 IU (one vial) of Cinryze should be injected up to 24 hours before a medical, dental, or surgical procedure.	*6 to 11 years:* A dose of 500 IU (one vial) of Cinryze should be injected every 3 or 4 days for routine prevention of swelling attacks. The dosing interval may be adjusted by your doctor depending upon your response to Cinryze.

Reconstitution and method of administration

Cinryze is usually injected into a vein (intravenously) by your doctor or nurse. You or your carer might also administer Cinryze as an injection, but only after receiving adequate training. If you are injecting Cinryze yourself, always use it exactly as your doctor has instructed you. Check with your

doctor if you are not sure. If your doctor decides that you may be suitable for such home-treatment, he/she will give you detailed instructions. You will be required to keep a diary in order to document each treatment received at home and to bring it to each of your visits to the doctor. Regular review of your/your carer's injection technique will be performed to ensure continued appropriate handling.

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

4. Possible side effects

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

This can include allergic-type reactions.

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

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

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

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

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

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

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland:
HPRA Pharmacovigilance
Website: www.hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cinryze

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

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

Once reconstituted, Cinryze solution should be used immediately.

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

6. Contents of the pack and other information

What Cinryze contains

The active substance is C1 inhibitor produced from the plasma of human donors. Each powder vial contains 500 IU of C1 inhibitor. After reconstitution, one vial contains 500 IU of C1 inhibitor (human) per 5 ml, corresponding to a concentration of 100 IU/ml. Two vials of reconstituted Cinryze contain 1000 IU of C1 inhibitor (human) per 10 ml, corresponding to a concentration of 100 IU/ml.

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

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

The other ingredients (excipients) are:
Powder vial: sodium chloride, sucrose, sodium citrate, L-valine, L-alanine and L-threonine. See section 2).
Solvent vial: water for injections.

What Cinryze looks like and contents of the pack

Cinryze is a white powder contained in a vial.

After it has been dissolved in the water for injections the solution is clear and colourless to slightly blue.

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

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

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder
Shire Services BVBA
Rue Montoyer 47
B - 1000 Brussels Belgium
medinfoeuceemea@shire.com

Manufacturer
Shire International Licensing B.V.
Strawinskylaan 481
1077 XX Amsterdam
The Netherlands

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

The following information is intended for healthcare professionals only:

Reconstitution and administration of Cinryze

Reconstitution, product administration and handling of the administration set and needles must be done with caution.

Use either the filter transfer device provided with Cinryze or a commercially available double-ended needle.

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

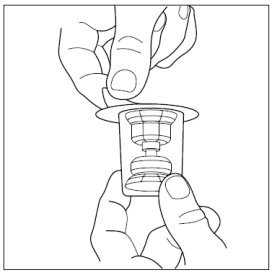
Preparation and handling
Cinryze is intended for intravenous administration (into the vein) after reconstitution with water for injections.
Cinryze vial is for single use only.

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

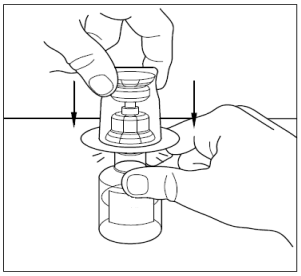
For a dose of 1000 IU: Two powder vials, 2 solvent vials, 2 filter transfer devices, 1 disposable 10 ml syringe, 1 venipuncture set and 1 protective mat are needed.

Each product vial should be reconstituted with 5 ml water for injections.
One vial of reconstituted Cinryze corresponds to a dose of 500 IU. Therefore only reconstitute one vial of Cinryze for one dose of 500 IU.
Two vials of reconstituted Cinryze correspond to a dose of 1000 IU. Therefore two vials are combined for one dose of 1000 IU.

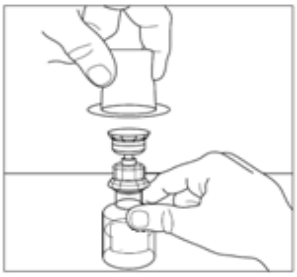
1. Work on the mat provided and wash your hands before performing the following procedures.
2. Aseptic technique should be used during the reconstitution procedure.
3. Ensure the powder vial and the solvent vial are at room temperature (15ºC - 25ºC).
4. Release the powder vial label by tearing down the perforated strip indicated by the inverted triangle.
5. Remove plastic caps from the powder and solvent vials.
6. Cleanse stoppers with a disinfection swab and allow them to dry prior to use.
7. Remove protective covering from the top of the transfer device package. Do not remove the device from the package.



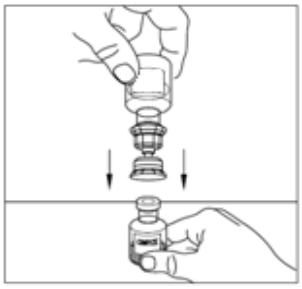
8. Note: the transfer device must be attached to the solvent vial before being attached to the powder vial, so that the vacuum in the powder vial is not lost. Place the solvent vial on a flat surface and insert the blue end of the transfer device into the solvent vial, pushing down until the spike penetrates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



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



10. Place the powder vial on a flat surface. Invert the transfer device and the solvent vial containing water for injections and insert the clear end of the transfer device into the powder vial, pushing down until the spike penetrates the rubber stopper and the transfer device snaps into place. The transfer device must be vertical prior to penetrating the stopper closure of the powder vial. The vacuum in the powder vial will draw in the solvent. If there is no vacuum in the vial, do not use the product.



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

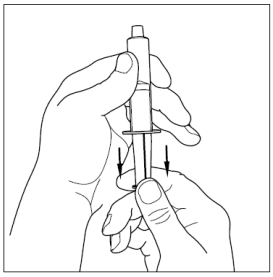
12. Disconnect the solvent vial by turning it anti-clockwise. Do not remove the clear end of the transfer device from the powder vial.

One vial of reconstituted Cinryze contains 500 IU of C1 inhibitor in 5 ml, resulting in a concentration of 100 IU/ml. Proceed to administration process if patients receive a dose of 500 IU.

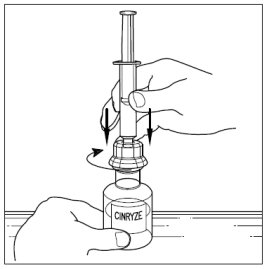
Two vials of Cinryze powder must be reconstituted to make one dose (1000 IU/10 ml). Therefore repeat instructions 1 to 12 above using an additional package containing a transfer device to reconstitute the second of two powder vials. Do not reuse the transfer device. Once the two vials are reconstituted proceed to administration process for a dose of 1000 IU.

Administration process for a dose of 500 IU

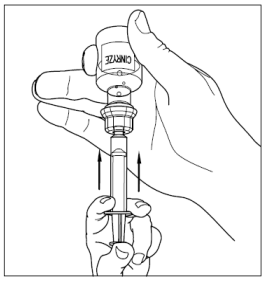
1. Aseptic technique should be used during the administration procedure.
2. After reconstitution, the Cinryze solutions are colourless to slightly blue and clear. Do not use the product if the solutions are turbid or discoloured.
3. Using a sterile, disposable 10 ml syringe, draw back the plunger to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

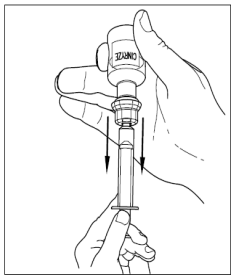


4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise.

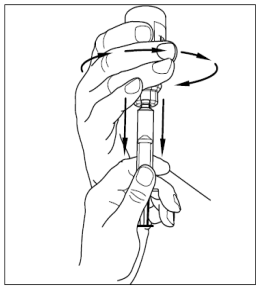
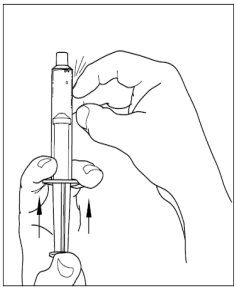


5. Invert the vial gently and inject air into the solution and then slowly withdraw the reconstituted Cinryze solution into the syringe.





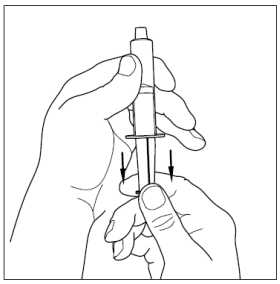
6. Detach the syringe from the vial by turning it anti-clockwise and releasing it from the clear end of the transfer device.

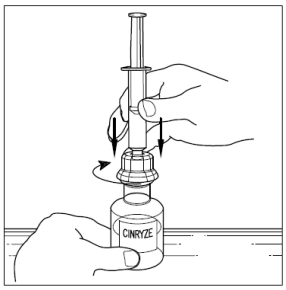
7. Inspect the reconstituted Cinryze solution for particulate matter prior to administration; do not use if particles are observed.
8. Attach the venipuncture set to the syringe containing Cinryze solution and inject intravenously (into the vein) into the patient. Administer 500 IU (reconstituted in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

Administration process for a dose of 1000 IU

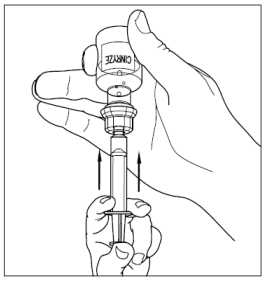
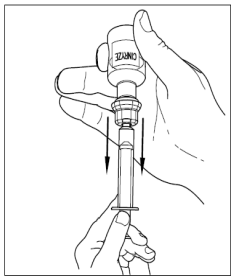
1. Aseptic technique should be used during the administration procedure.
2. After reconstitution, the Cinryze solutions are colourless to slightly blue and clear. Do not use the product if the solutions are turbid or discoloured.
3. Using a sterile, disposable 10 ml syringe, draw back the plunger to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



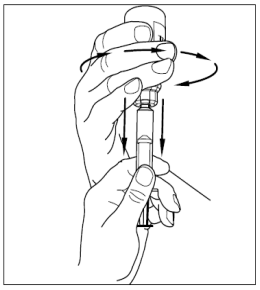
4. Attach the syringe onto the top of the clear end of the transfer device by turning it clockwise.

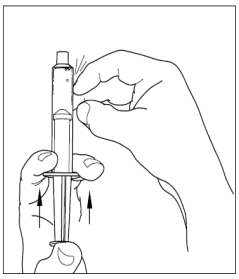


5. Invert the vial gently and inject air into the solution and then slowly withdraw the reconstituted Cinryze solution into the syringe.

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





7. Using the same syringe, repeat steps 3 to 6 with a second vial of reconstituted Cinryze to make one complete 10 ml dose.
8. Inspect the reconstituted Cinryze solution for particulate matter prior to administration; do not use if particles are observed.
9. Attach the venipuncture set to the syringe containing Cinryze solution and inject intravenously (into the vein) into the patient. Administer 1000 IU (reconstituted in 10 ml of water for injections) of Cinryze by intravenous injection (into the vein) at a rate of 1 ml per minute over 10 minutes.

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