A. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ruconest 2100 Units powder and solvent for solution for injection
conestat alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ruconest is and what it is used for
2. What you need to know before you use Ruconest
3. How to use Ruconest
4. Possible side effects
5. How to store Ruconest
6. Contents of the pack and other information

1. What Ruconest is and what it is used for

Ruconest contains conestat alfa as the active substance. Conestat alfa is a recombinant (not blood-derived) form of human C1 inhibitor (rhC1-INH).

Ruconest is to be used by adults, adolescents, and children (aged 2 years and above) with a rare inherited blood disorder, called Hereditary Angioedema (HAE). These patients have a shortage of the C1 inhibitor protein in their blood. This can lead to repeated attacks of swelling, pain in the abdomen, difficulty breathing and other symptoms.

The administration of Ruconest is to resolve the shortage of C1 inhibitor and will lead to reduction of symptoms of an acute attack of HAE.

2. What you need to know before you use Ruconest

Do not use Ruconest
- If you are or think you are allergic to rabbits.
- If you are allergic to conestat alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before using Ruconest.
If you experience allergic reactions e.g. hives, rash, itching, dizziness, wheezing, difficulty breathing or your tongue swells up following the administration of Ruconest, you should seek emergency medical assistance so that symptoms of your allergic reaction can be treated urgently.

Before you start treatment with Ruconest, 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.

Hypersensitivity reactions cannot be excluded and may have symptoms similar to angioedema attacks.

Children and adolescents
Do not give this medicine to children under 2 years old. Ruconest has not been studied in children younger than 5 years of age. Your doctor will determine whether treatment of your child with Ruconest is appropriate. Additional monitoring of your child for symptoms of allergic reactions during and after administration is needed.

Other medicines and Ruconest
Tell your doctor if you are taking, have recently taken or might take any other medicines.
If you are receiving tissue type plasminogen activator as acute treatment for blood clots, you should not be treated with Ruconest at the same time.

Pregnancy and breast-feeding
It is not recommended to use Ruconest during pregnancy or breast-feeding.
If you plan becoming pregnant, discuss with your doctor before starting to use Ruconest.

Driving and using machines
Do not drive or use machinery if you feel dizzy or suffer from headache after using Ruconest.

Ruconest contains sodium (19.5 mg per vial)
This should be taken into consideration by patients on a controlled sodium diet.

3. How to use Ruconest

Ruconest will be initiated by a doctor who is specialised in the diagnosis and treatment of hereditary angioedema.

Ruconest must be administered by a healthcare professional until you or your caregiver are properly trained and capable to administer Ruconest.

Always use this medicine exactly as described in this leaflet or as your doctor or nurse have told you. Check with your doctor or nurse if you are not sure.

Ruconest is administered into a vein over about 5 minutes. Your dose will be worked out based on your body weight.

Most of the time a single dose is sufficient. An additional dose could be administered if your symptoms do not improve after 120 minutes (for adults and adolescents) or 60 minutes (for children). No more than 2 doses, calculated according to step 7, should be given within 24 hours.

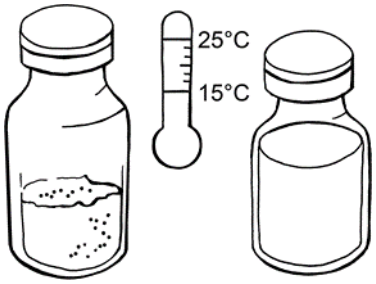
You or your caregiver may inject Ruconest only after receiving adequate instructions and training from your doctor or nurse.

Instructions for use
Do not mix or administer Ruconest with other medicines or solutions. The following describes how Ruconest solution must be prepared and administered.

Before you begin
- Ensure the kit package is complete and contains all components listed in section 6 of this leaflet.
- In addition to the kit, the following is required:
  - a tourniquet
  - plaster for securing the needle
- Inspect vials and other components.
  - All vials must be sealed with plastic lid and aluminium cap and without visible damage, such as cracks in glass.
  - Check the expiry date. Never use any kit component after the expiry date stated on the big outer carton.
    Within a single kit box, different components may have different expiry dates. The expiry date on

the outer carton reflects the date of the component with the shortest shelf-life.

- Allow the number of powder and solvent vials required according to step 1, to reach room temperature.



Preparation of solution

Step 1: Cleaning and other requirements

- Wash your hands carefully.
- Put the powder and solvent vials required on a flat and clean surface.
  - body weight 42 kg or less: 1 powder and 1 solvent vial
  - body weight over 42 kg: 2 powder and 2 solvent vials
- Put the vial adapters on the work surface. Do not remove the adapter packaging.
  - 2 adapters if 1 powder and 1 solvent vial is required
  - 4 adapters if 2 powder and 2 solvent vials are required
- Put the syringe(s) on the work surface. Do not remove the syringe packaging.
  - 1 syringe if 1 powder and 1 solvent vial is required
  - 2 syringes if 2 powder and 2 solvent vials are required

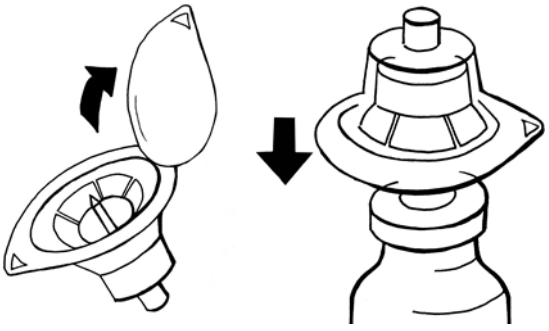
Step 2: Disinfection of vial stoppers

- Remove the plastic flip-off cap from the powder and solvent vials.
- Use one alcohol pad to disinfect all vial stoppers and wait for at least 30 seconds until the stoppers have dried.

- After disinfection, do not touch the stoppers with your fingers or anything else.

Step 3: Mounting of adapters on vials

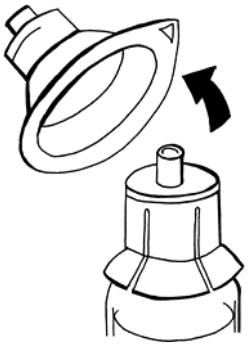
- Take a packaged adapter in one hand and remove the lid. The adapter must remain in its plastic packaging.
- Put the adapter onto a powder vial, piercing the stopper, until it snaps onto the vial neck.



- Leave the packaging on the adapter until you attach the syringe in steps 4 and 5.
- Repeat the above steps for mounting an adapter on the solvent vial. All adapters supplied with the kit are identical.
- If you need to use a second powder and solvent vial, repeat the above steps.

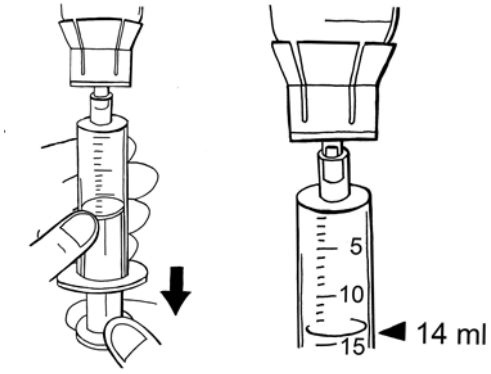
Step 4: Drawing up solvent

- Take a sterile syringe out of its packaging.
- Remove the packaging from the adapter on the solvent vial.



- Hold the adapter with one hand. With the other hand, attach the syringe and secure by turning it clockwise until it stops.

- Turn the whole – solvent vial with adapter and syringe – upside down. While keeping it vertical, slowly draw in 14 ml solvent.
  If air bubbles appear, minimise as far as possible by gently tapping the syringe and applying gentle pressure by pushing the plunger into the syringe. Continue to fill the syringe with 14 ml solvent.

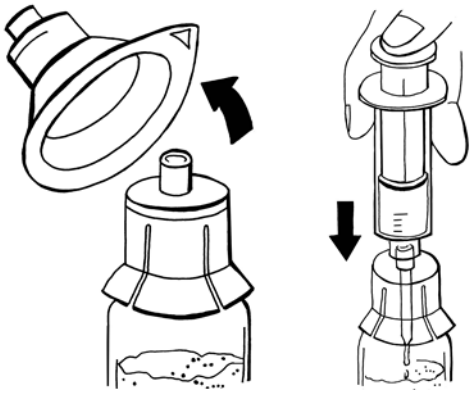


- Unlock the syringe from the adapter by turning counter-clockwise.

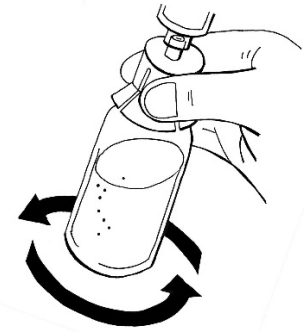
- Leave the remainder of the solvent in the vial and discard the vial.
- Place the syringe on the work surface, taking care not to touch the surface or any other object with the syringe tip.

Step 5: Adding solvent to powder and dissolving

- Remove the packaging from the adapter on the powder vial.
- Take the syringe with solvent that you prepared in step 4.
- Hold the adapter with the other hand and attach the syringe. Secure the syringe by turning it clockwise until it stops.
- Push the solvent slowly, in a single motion, into the powder vial in order to minimise foaming.



- Leave the syringe on the adapter and gently swirl the vial for approximately half a minute. Do not shake.
  After swirling, leave the vial on the surface for several minutes until the solution has become clear. If undissolved powder is still present, repeat the procedure.

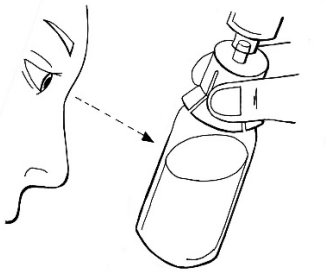


- Repeat steps 4 and 5 if you need to prepare a second solution.

Step 6: Check prepared solutions

- Check whether the powder in the vial(s) has dissolved completely and the plunger is completely pushed down in the syringe.
- After the powder has dissolved, the solution should be clear and colourless.
- Do not use the prepared solution if it is cloudy, contains particles or has changed colour. Inform your

healthcare professional if this occurs. Small amounts of foam are acceptable.



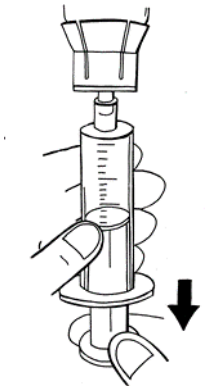
Step 7: Drawing up prepared solution

- Calculate the millilitres of prepared solution to be injected.

Body weight	Millilitres of prepared solution to be injected
below 84 kg	Body weight in kg divided by three
84 kg and above	28 ml

- Draw in the volume of prepared solution, while keeping the syringe in the vertical position. If you have prepared:
  - one vial with solution, draw up the volume as calculated
  - two vials and your body weight is below 84 kg, draw up in a similar way:
    a) 14 ml from the first vial
    b) from the second vial, the difference between your calculated volume and the 14 ml from the first vial
  - two vials and your body weight is 84 kg or more, draw up 14 ml from each vial into each syringe

  If air bubbles appear, minimise as far as possible by gently tapping the syringe and applying gentle pressure by pushing the plunger into the syringe. Continue to fill the syringe with the volume required.



- Never exceed the volume of 14 ml per syringe.
- Unlock the syringe(s) by turning it counter-clockwise and discard the vial(s) with adapter.
- Place the syringe(s) on the work surface, taking care not to touch the surface or any other object with the syringe tip.

Step 8: Check prepared syringes

- Recheck that the volume in the syringe(s) you prepared in step 7 is correct.

Administration into a vein

It is very important that the prepared solution is injected directly into a vein and not into an artery or the surrounding tissue.

Inject the Ruconest solution immediately after preparation, preferably while seated.

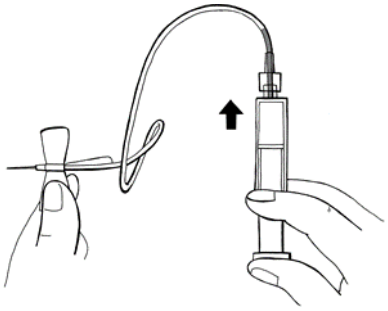
Step 9: Required components

- Check that all required components are on the work surface:
  - 1 or 2 syringes with prepared solution
  - 1 infusion set with 25G needle

- 1 alcohol pad
- 1 sterile non-woven pad
- 1 self-adhesive plaster
- 1 tourniquet
- 1 plaster for securing the needle

Step 10: Preparation of the infusion set

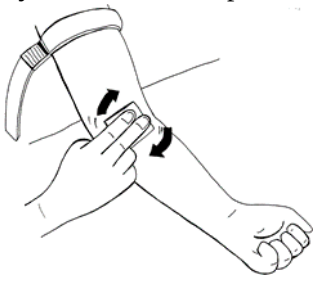
- Remove the screw cap from the end of the infusion set. This is the end which has no needle.
- Hold this end with one hand, attach the syringe tip end and secure by turning clockwise until it stops.
- Hold the syringe with the tip pointing upwards. Gently press the syringe plunger to carefully fill the infusion set with the prepared solution.



- Check that no air is present in the syringe, infusion tube or the needle.

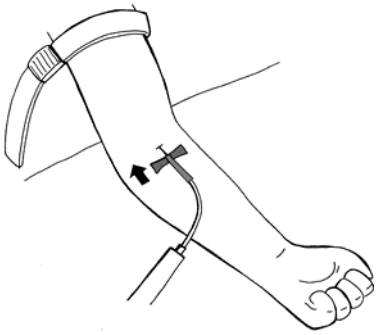
Step 11: Preparing the injection site

- Position the tourniquet above the injection site – preferably the middle part of the upper arm. Tighten it to compress the vein. This should be boosted by tightening your fist.
- Feel, with your other hand, for an appropriate vein.
- Disinfect the injection site thoroughly with an alcohol pad and let the skin dry.



Step 12: Administration of the prepared solution

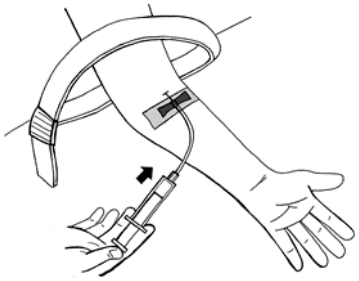
- Remove the needle cap.
- Carefully insert the needle of the infusion set, at the flattest possible angle, into the vein.



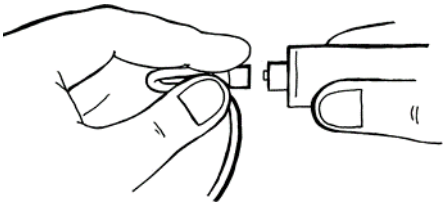
- Secure the needle by applying the plaster, around 7 cm long, over the wings of the needle.
- Carefully pull back the syringe plunger slightly until you see blood being drawn into the tubing, to ensure that the needle is in the vein.
- Release the tourniquet.
- If there is no blood in the tubing, remove the needle, repeat all steps from beginning of step 11 and

reposition the needle.

- If blood is present, gently inject the solution into the vein, as shown in the picture. Inject over about 5 minutes.



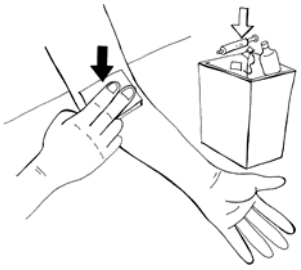
- If you have prepared two syringes:
  - fold over the tubing near the connector of the infusion set to prevent backflow
  - unscrew the empty syringe from the infusion set and immediately replace it with the second syringe



  - unfold the tubing and gently inject this solution, similar to the first syringe

Step 13: After administration

- Carefully remove the plaster for securing the needle and withdraw the needle from the vein.
- Immediately after removing the needle, press the sterile pad on the injection site for a few minutes to reduce bleeding.



- Next, put the self-adhesive plaster on the injection site.
- Fold down the yellow protection cap over the needle.
- Safely dispose of the used infusion set with needle, any unused solution, the syringe and the empty vial in an appropriate medical waste container as these materials may hurt others if not disposed of properly. Do not reuse equipment.

Step 14: Documenting the administration
Please record (e.g. in your diary):

- date and time of the administration
- the batch number written on the label of the powder vial

If you use more Ruconest than you should
Contact your doctor or nearest hospital if this occurs.

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

4. Possible side effects

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

If your symptoms get worse and/or you develop a rash, tingling, difficulty breathing or your face or tongue swells up, get medical attention **immediately**. **This may indicate that you have developed an allergy to Ruconest.**

Some side effects may occur during treatment with Ruconest:
Common: may affect up to 1 in 10 people
- Nausea

Uncommon: may affect up to 1 in 100 people
- Abdominal pain, diarrhoea
- Sensation of tingling, prickling or numbness in the mouth
- Headache, dizziness
- Reduced sense of touch or sensation in skin or limbs
- Throat irritation
- Hives
- Swelling of the ears or the area around the ears
- Allergic shock

Not known: the frequency is not known
- Hypersensitivity reactions

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

United Kingdom (Northern Ireland)
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

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

For any patients who do not have online access to report a suspected side effect to the Yellow Card scheme, call 0800 731 6789 for free, Monday to Friday between 10am and 2pm.

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

5. How to store Ruconest

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

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after

EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.
Keep the powder vial in the vial carton in order to protect from light.

Before Ruconest can be administered, the powder needs to be dissolved in the solvent included in the package (see section 3).
Once reconstituted, the product should be used immediately.
Do not use this medicine if, after dissolving, you notice particles in the solution or if the solution is discoloured. Small amounts of foam are acceptable.

6. Contents of the pack and other information

What Ruconest contains
Powder vial:
- The active substance is conestat alfa. Each powder vial contains 2100 units of conestat alfa, corresponding to 2100 units per 14 ml after reconstitution, or a concentration of 150 units/ml.
- The other ingredients of the powder are sucrose, sodium citrate (E331) and citric acid.

Solvent vial:
- The ingredient of the solvent is water for injections.

What Ruconest looks like and contents of the pack
Ruconest is presented as a single glass vial containing a white to off-white powder for solution for injection together with one glass vial containg a clear, colourless solvent to dissolve the powder. After dissolving the powder in water for injections, the solution is clear and colourless.

Ruconest is supplied with an administration kit in a carton box containing:
- 1 vial of 2100 U powder
- 1 vial of 20 ml solvent
- 2 vial adapters
- 1 syringe
- 1 infusion set with 35 cm tubing and 25G needle
- 2 alcohol pads
- 1 sterile non-woven pad
- 1 self-adhesive plaster

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Pharming Group N.V.
Darwinweg 24
2333 CR Leiden
The Netherlands

Manufacturer:
Pharming Technologies B.V.
Darwinweg 24
2333 CR Leiden
The Netherlands

This leaflet was last revised in July 2023.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Body weight up to 84 kg

- One intravenous injection of 50 U/kg body weight.

Body weight of 84 kg or greater

- One intravenous injection of 4200 U (two vials).

In the majority of cases a single dose of Ruconest is sufficient to treat an acute angioedema attack.
In case of an insufficient clinical response, an additional dose (50 U/kg body weight up to 4200 U) can be administered.
Not more than two doses should be administered within 24 hours.

Dose calculation

Determine the patient's body weight.

Body weight up to 84 kg

- For patients up to 84 kg calculate the volume required to be administered according to the formula below:

$$\textbf{Volume to be administered (ml)} = \frac{\textbf{body weight (kg) times 50 (U/kg)}}{\textbf{150 (U/ml)}} = \frac{\textbf{body weight (kg)}}{\textbf{3}}$$

Body weight of 84 kg or greater

- For patients of 84 kg or above the volume required to be administered is 28 ml, corresponding to 4200 U (2 vials).

Reconstitute *each vial* with 14 ml water for injections (see section on Reconstitution below).
The reconstituted solution in each vial contains 2100 U conestat alfa at 150 U/ml.

The required volume of the reconstituted solution should be administered as a slow intravenous injection over approximately 5 minutes.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation and handling

Each vial of Ruconest is for single use only.
Ruconest is intended for intravenous administration after reconstitution with water for injections. An aseptic technique should be used for reconstitution, combining and mixing the solutions.

Reconstitution

1. Each vial of Ruconest (2100 U) should be reconstituted with 14 ml water for injections.

2. Disinfect the rubber stoppers of the powder and solvent vials and put a vial adapter onto each solvent and powder vial until it snaps onto the vial neck.
3. Attach a syringe to the adapter on a solvent vial and turn clockwise until it locks. Draw in 14 ml of solvent. Unlock the syringe from the adapter by turning counter clockwise. Repeat this step if two powder vials need to be reconstituted.
4. Attach a syringe with solvent to the adapter on a powder vial and turn clockwise until it locks. Water for injections should be added slowly to avoid forceful impact on the powder and mixed gently to minimise foaming of the solution. Leave the syringe on the adapter. Repeat this step if a second powder vial needs to be reconstituted.
5. The reconstituted solution in each vial contains 150 U/ml and appears as a clear colourless solution. The reconstituted solution in each vial should be inspected for particulate matter and discoloration. A solution exhibiting particulates or discoloration should not be used. Small amounts of foam are acceptable. The medicinal product should be used immediately.

Administration

1. Draw in the required volume of prepared solution. Never exceed 14 ml per syringe. Unlock the syringe(s) by turning counter clockwise and discard vial(s) with adapter
2. Attach the infusion set to the syringe and turn clockwise until it locks. Hold the syringe with the tip pointing upwards and gently press the plunger to fill the infusion set with the solution
3. Disinfect the injection site with an alcohol pad. Remove the needle cap from the needle of the infusion set and carefully insert the needle into the vein.
4. Ensure that the tourniquet is released. Gently inject the solution into the vein – inject over about 5 minutes.
5. If two syringes were prepared: fold over the tubing to prevent backflow, unscrew the empty syringe from the infusion set (counter clockwise) and immediately replace it with the second syringe. Gently inject the solution of the second syringe.

Disposal

Please safely dispose of the used infusion set with needle, any unused solution, the syringe and the empty vial in an appropriate medical waste container as these materials may hurt others if not disposed of properly.

Do not reuse equipment.