1. NAME OF THE MEDICINAL PRODUCT

Ruconest - powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 2100 units of conestat alfa, corresponding to 2100 units per 14 ml after reconstitution, or a concentration of 150 units/ml.

Conestat alfa is a recombinant analogue of the human C1 esterase inhibitor (rhC1-INH) produced by recombinant DNA technology in the milk of transgenic rabbits.

1 unit of conestat alfa activity is defined as the equivalent of C1 esterase inhibiting activity present in 1 ml of pooled normal plasma.

Excipient with known effect:
Each vial contains approximately 19.5 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ruconest is indicated for treatment of acute angioedema attacks in adults and adolescents aged 12 years and above with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.

4.2 Posology and method of administration

Ruconest should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of hereditary angioedema.

Posology in adults and adolescents aged 12 years and above

- *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 (2 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 at the discretion of the physician (see section 5.1).

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:

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

- *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).

Paediatric population
The safety and efficacy of Ruconest in children (age 0 to 12 years) have not yet been established..

Elderly (≥65 years old)
Data in patients older than 65 years are limited.
There is no rationale for patients older than 65 years to respond differently to Ruconest.

Renal impairment
No dose adjustment is necessary in patients with renal impairment since conestat alfa does not undergo renal clearance.

Hepatic impairment
There is no clinical experience with Ruconest in patients with hepatic impairment. Hepatic impairment may prolong the plasma half-life of conestat alfa, but this is not thought to be a clinical concern. No recommendation on a dose adjustment can be made.

Method of administration

For intravenous use.
Ruconest should be administered by a healthcare professional.
For instructions on reconstitution of Ruconest before administration, see section 6.6.
The required volume of the reconstituted solution should be administered as a slow intravenous injection over approximately 5 minutes.

4.3 Contraindications

- Known or suspected allergy to rabbits (see section 4.4)
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered products should be clearly recorded.

Conestat alfa is derived from milk of transgenic rabbits and contains traces of rabbit protein. Before initiating treatment with Ruconest, patients should be queried about prior exposure to rabbits and signs and symptoms suggestive of an allergic reaction.

Hypersensitivity reactions cannot be excluded.
All patients must be closely monitored and carefully observed for any symptoms of hypersensitivity during and after the administration period. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur after administration, they should alert their physician.
In case of anaphylactic reactions or shock, emergency medical treatment should be administered.

Although cross-reactivity between cow milk and rabbit milk is considered unlikely, the possibility of such a cross-reactivity in a patient who has evidence of clinical allergy to cow milk cannot be excluded and the patient should be observed for signs and symptoms of hypersensitivity following Ruconest administration.

Sodium
Each vial of Ruconest contains 19.5 mg of sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Scientific literature indicates an interaction of tissue-type plasminogen activator (tPA) and C1-INH containing medicinal products. Ruconest should not be administered simultaneously with tPA.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
There is no experience with the use of Ruconest in pregnant and breast-feeding women.
In one animal study reproductive toxicity was observed (see section 5.3). Ruconest is not recommended for use during pregnancy or breast-feeding, unless the treating physician judges the benefits to outweigh the possible risks.

Fertility
There are no data on the effects of Ruconest on male or female fertility.

4.7 Effects on ability to drive and use machines

Based on the known pharmacology and adverse reaction profile of Ruconest, effects on the ability to drive and use machines are not expected. However, headache, vertigo and dizziness have been reported following the use of Ruconest, but may also occur as a result of an attack of HAE. Patients should be advised not to drive and use machines if they experience headache, vertigo or dizziness.

4.8 Undesirable effects

Summary of the safety profile
One case of hypersensitivity was observed in clinical trials with Ruconest. The most common adverse reaction observed after administration of Ruconest is nausea .

Tabulated lists of adverse reactions
Adverse reactions obtained from clinical trials in patients with HAE following acute attack treatment with Ruconest are tabulated below.

Adverse reactions were usually mild to moderate in severity. The incidence of adverse reactions was similar for all dose groups and did not increase upon repeated administration.

The frequency of adverse reactions listed below is defined using the following convention:
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),
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

System Organ Class	**Adverse reaction**	**Frequency**
Nervous system disorders	Headache	Uncommon
	Vertigo	Uncommon
	Hypoaesthesia	Uncommon
	Dizziness	Uncommon
Ear and labyrinth disorders	Auricular swelling	Uncommon
Respiratory, thoracic and mediastinal disorders	Throat irritation	Uncommon
Gastrointestinal disorders	Nausea	Common
	Diarrhoea	Uncommon
	Abdominal discomfort	Uncommon
	Oral paraesthesia	Uncommon
Skin and subcutaneous tissue disorders	Urticaria	Uncommon

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
Additionally, you should also report to Kamada Ltd. to email address:
pharmacovigilance@kamada.com

4.9 Overdose

No clinical information on overdose is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, drugs used in hereditary angioedema, ATC code: B06AC04.

The plasma protein C1-INH is the main regulator of activation of the contact and complement systems *in vivo*. HAE patients have a heterozygous deficiency of the plasma protein C1-INH. As a result they may suffer from uncontrolled activation of contact and complement systems, with formation of inflammatory mediators, which clinically becomes manifest as the occurrence of acute angioedema attacks.

Conestat alfa, a recombinant human complement component 1 (C1) esterase inhibitor (rhC1-INH), is an analogue of human C1-INH and is obtained from the milk of rabbits expressing the gene coding for human C1-INH. The amino acid sequence of conestat alfa is identical to that of endogenous C1-INH.

C1-INH exerts an inhibitory effect on several proteases (target proteases) of the contact and complement systems. The effect of conestat alfa on the following target proteases was assessed *in vitro*: activated C1s, kallikrein, factor XIIa and factor XIa. Inhibition kinetics were found to be comparable with those observed for plasma-derived human C1-INH.

The complement component (protein) C4, is a substrate for activated C1s. Patients with HAE have low levels of C4 in the circulation. As for plasma-derived C1-INH, the pharmacodynamic effects of conestat alfa on C4 show dose-dependent restoration of complement homeostasis in HAE patients at a plasma C1-INH activity level greater than 0.7 U/ml, which is the lower limit of the normal range. In HAE patients, Ruconest at a dose of 50 U/kg increases plasma C1-INH activity level to greater than 0.7 U/ml for approximately 2 hours (see section 5.2).

The efficacy and safety of Ruconest as a treatment of acute angioedema attacks in adult and adolescent patients with HAE has been evaluated in two double blind randomized placebo controlled and four open label clinical studies. The doses evaluated in the clinical studies ranged from a single vial of 2100 U (corresponding to 18-40 U/kg), to 50 and 100 U/kg. Efficacy of Ruconest as a treatment for acute angioedema attacks was demonstrated by significantly shorter time to beginning of relief of symptoms and time to minimal symptoms and few therapeutic failures. The table below shows the results (primary and secondary endpoints) of the two randomized controlled trials:

Study	Treatment	Time (minutes) to beginning of relief median (95% CI)	Time (minutes) to minimal symptoms median (95% CI)
C1 1205 RCT	100 U/kg n =13	68 (62, 132) p = 0.001	245 (125, 270) p = 0.04
	50 U/kg n =12	122 (72, 136) p < 0.001	247 (243, 484)
	Saline n = 13	258 (240, 495)	1101 (970, 1494)
C1 1304 RCT	100 U/kg n =16	62 (40, 75) p = 0.003	480 (243, 723) p = 0.005
	Saline n = 16	508 (70, 720)	1440 (720, 2885)

The results of the open label studies were consistent with the above findings and support the repeated use of Ruconest in the treatment of subsequent attacks of angioedema.

In the randomized controlled trials 39/41 (95%) of patients treated with Ruconest reached time to beginning of relief within 4 hours. In an open label study 146/151 (97%) attacks treated with a single dose of 50 U/kg reached time to beginning of relief within 4 hours. An additional dose of 50 U/kg was administered for 17/168 (10%) attacks.

Paediatric population

Adolescents
Ten adolescent HAE patients (aged 13 to 17 years) were treated with 50 U/kg for 27 acute angioedema attacks, and 7 (aged 16 to 17 years) with 2100 U for 24 acute angioedema attacks.
The efficacy and safety results in adolescents were consistent with those in adults.

The European Medicines Agency has deferred the obligation to submit the results of studies with Ruconest in one or more subsets of the paediatric population in treatment of acute angioedema attacks (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Distribution
No formal distribution studies have been performed. The distribution volume of conestat alfa was approximately 3 L, comparable to plasma volume.

Biotransformation and elimination
Based on animal data, conestat alfa is cleared from the circulation by the liver via receptor-mediated endocytosis followed by complete hydrolysis/degradation.

After administration of Ruconest (50 U/kg) to asymptomatic HAE patients, a C_{max} of 1.36 U/ml was observed. The elimination half-life of conestat alfa was approximately 2 hours.

Excretion
There is no excretion, as conestat alfa is cleared from the circulation via receptor-mediated endocytosis followed by complete hydrolysis/degradation in the liver.

5.3 Preclinical safety data

Preclinical data do not indicate any safety concern for the use of conestat alfa in humans based on studies of safety pharmacology, single-dose toxicity, two-week sub-chronic toxicity and local tolerance in various animal species including rats, dogs, rabbits and cynomolgus monkeys. Genotoxic and carcinogenic potential is not expected.

Embryofoetal studies in rat and rabbit; Daily single doses of vehicle or 625 U/kg/administration of conestat alfa were administered intravenously to mated rats and rabbits. In the study in rats there were no malformed foetuses in either the conestat alfa or the control group. In a rabbit embryotoxicity study an increase in the incidence of foetal cardiac vessel defects (1.12% in the treatment group versus 0.03% in historical controls) was observed for animals that were administered conestat alfa.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate dihydrate
Citric acid monohydrate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials
Reconstituted solution
Reconstituted drug product is stable for 48 hours when stored between 5˚C and 25˚C. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2100 units of conestat alfa powder in a 25 ml vial (type 1 glass) with a stopper (siliconized chlorobutyl rubber) and a flip-off seal (aluminium and coloured plastic).
Pack size of 1.

6.6 Special precautions for disposal and other handling

Each vial of Ruconest is for single use only.
An aseptic technique should be used for reconstitution, combining and mixing the solutions.

Reconstitution
Each vial of Ruconest (2100 U) should be reconstituted with 14 ml water for injections. Water for injections should be added slowly to avoid forceful impact on the powder and mixed gently to minimise foaming of the solution. The reconstituted solution contains 150 U/ml conestat alfa and appears as a clear colourless solution.

The reconstituted solution in each vial should be visually inspected for particulate matter and discoloration. A solution exhibiting particulates or discoloration should not be used. The medicinal product should be used immediately (see section 6.3).

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

7. MARKETING AUTHORISATION HOLDER

Kamada Ltd
BEIT KAMA, Israel

8. MANUFACTURER

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