HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 March 2011

RUCONEST 2100 U, powder for solution for injection
B/1 (CIP code: 498 941-0)

Applicant: SWEDISH ORPHAN BIOVITRUM

Conestat alfa
ATC code: B06AC04

List I
Medicinal product reserved for hospital use.
Before initiating treatment with RUCONEST, patients should be tested for the presence of IgE antibodies against rabbit allergens. Only patients who have been shown to have negative results for such a test should be treated with RUCONEST. IgE antibody testing should be repeated once a year or after 10 treatments.

Date of Marketing Authorisation: 28 October 2010 (centralised Marketing Authorisation, rapporteur country = United Kingdom)

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Conestat alfa

1.2. Background
The active ingredient of RUCONEST, conestat alfa, is the first recombinant analogue of the human C1 esterase inhibitor (rhC1INH) produced by recombinant DNA technology in the milk of transgenic rabbits.

1.3. Indication
"RUCONEST is indicated in the treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency."

1.4. Dosage
"RUCONEST should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of hereditary angioedema.
RUCONEST should be administered by a healthcare professional.

Patients who have not previously received RUCONEST should be tested for the presence of IgE antibodies against rabbit epithelium (dander) prior to initiation of RUCONEST (see section 4.4).

Dosage
- *Adults up to 84 kg body weight:* one intravenous injection of 50 U/kg body weight.
- *Adults of 84 kg body weight 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 (see section 5.1). Not more than two doses should be administered within 24 hours.

Dose calculation: Determine the patient's body weight.

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

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

Adults of 84 kg body weight 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 tolerance and efficacy of RUCONEST in children (age 0 to 12 years) have not yet been established. Currently available data on adolescents (age 13 to 17 years) are described in section 5.1, but no recommendation on dosage can be made.

Elderly patients (≥ 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. For instructions on reconstitution of RUCONEST before administration, see section 6.6 of the SPC. The required volume of the reconstituted solution should be administered as a slow intravenous injection over approximately 5 minutes."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

B06AC04: Temporary ATC code provided by the company, not given in the Marketing Authorisation.

2.2. Medicinal products in the same therapeutic category

These are the other C1 esterase inhibitors indicated in the treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency:

- BERINERT (C1 esterase inhibitor, human)

2.3. Medicinal products with a similar therapeutic aim

Medicines used in hereditary angioedema attacks:

- EXACYL (tranexamic acid): off-label use,
- FIRAZYR (icatibant)

Medicine indicated for prophylactic therapy in patients with hereditary angioedema:

- DANATROL 200 mg (danazol)

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and tolerance of RUCONEST have been evaluated in 6 clinical trials:

- 2 pivotal phase II (trial 1205) and III (trial 1304) randomised double-blind trials, the aim of which was to compare the efficacy of RUCONEST with that of placebo in terms of time to relief of symptoms of angioedema attacks, and the open extension phase of each trial (1205 OLE and 1304 OLE)
- 4 open phase I, II and II/III studies, the aim of which was to determine the efficacy and tolerance of RUCONEST in relation to dose administered in healthy volunteers (n=14) or patients with HAE (n=26). These trials will not be included in this opinion in view of their design.

3.1.1. Trial 1205

Design: phase II comparative randomised double-blind trial of RUCONEST 50 U/kg versus RUCONEST 100 U/kg versus placebo, in 38 patients with hereditary angioedema (HAE).

Inclusion criteria: patients aged over 12 years with C1 inhibitor (C1-INH) concentration <50% of normal and having an HAE attack:

- within the last five hours,
- of severity defined on a visual analogue scale (VAS)[1] of ≥ 50 mm at H-1,
- with no improvement in HAE symptoms between H-1 and H0, improvement being defined as a decrease ≥ 20 mm on the VAS.

Severe forms (laryngeal oedema) were not included as the trials were placebo-controlled.

Treatment:

- RUCONEST 50 U/kg, infusion, n=12,
- RUCONEST 100 U/kg, infusion, n=13,
- Placebo, n=13.

Primary efficacy endpoint: median time (minutes) to improvement in HAE attack symptoms after a single dose of treatment, defined as improvement of at least 20 mm in VAS score.

RESULTS: *see Table 1*
Patient characteristics were comparable on inclusion.

Table 1: time in minutes to relief of symptoms (improvement of at least 20 mm in VAS score)

	RUCONEST 50 U/kg n=12	RUCONEST 100 U/kg n=13	Placebo n=13
median time to symptom relief (minutes)	122 [72 – 136]	68 [62 – 132]	258 [240 – 495]
p versus placebo	0.001	0.001	

After one injection, there was a significant reduction in median time to relief of symptoms with RUCONEST 50 and 100 U/kg compared with placebo: 122 minutes [72 – 136] for RUCONEST 50 U/kg, 68 minutes [62 – 132] for RUCONEST 100 U/kg versus 258 minutes [240 – 495] for placebo, p=0.001.

1 Visual analogue scale from 0 to 100: 0 = no symptoms, 100 = extremely incapacitating

Open follow-up study: study 1205 OLE

During the open follow-up period (6 months), 21 patients with HAE were treated for a total of 35 acute angioedema attacks with an initial dose of RUCONEST 50 U/kg. Median times to relief of symptoms (improvement in VAS score) are summarised in the table below:

	1st attack (N=27)	**2nd attack (N=25)**	**3rd attack (N=13)**	**4th attack (N=7)**	**5th attack (N=4)**
median time (minutes) (95% CI)	64 [56; 88]	63 [41; 67]	52 [37; 65]	242 [40; 271]	106.5 [20; ND]

This study appears to show that the efficacy of RUCONEST is maintained up to the third attack; from the fourth attack, median time to relief of symptoms increased. These results should be interpreted with caution in view of the small number of patients followed-up.

3.1.2. Trial 1304

Design: Phase III comparative, randomised, double-blind, placebo-controlled study of RUCONEST 100 U/kg in 32 patients with hereditary angioedema (HAE).

Inclusion criteria: patients aged over 16 years with type 1 HAE and C1 inhibitor (C1-INH) concentration <50% of normal and having an HAE attack:

- within the last five hours,
- of severity defined on a VAS of ≥50 mm at H-1,
- with no improvement in HAE symptoms between H-1 and H0, improvement being defined as a decrease ≥ 20 mm on the VAS.

Severe forms (laryngeal oedema) were not included because of the comparison with placebo.

Treatment:

- RUCONEST 100 U/kg, infusion, n=16,
- Placebo, n=16.

Primary efficacy endpoint: median time (minutes) to improvement in HAE attack symptoms after a single dose of treatment, defined as improvement in VAS score of ≥20 mm to ≥50 mm.

RESULTS: *see Table 1*

Patient characteristics were comparable on inclusion.

Mean weight on inclusion of patients treated with RUCONEST 100 U/kg was 84.16 Kg which implies that an unspecified number of patients weighing less than 84 kg were treated with RUCONEST 100 U/kg (double the dosage in the Marketing Authorisation).

Table 1: time in minutes to relief of symptoms (improvement in VAS score of ≥50 mm to ≥20 mm)

	RUCONEST 100 U/kg n=16	Placebo n=16
median time to symptom relief (minutes)	61.5 [40 – 75]	508 [70 – 720]
p versus placebo	0.003	

After one injection, there was a significant reduction in median time to relief of symptoms with RUCONEST 100 U/kg compared with placebo: 61.5 minutes [40-75] for RUCONEST 100 U/kg versus 508 minutes [70 -720] for placebo, p=0.003.

Time to relief of symptoms with placebo was significantly longer in trial 1304 than in trial 1205; when the EMA asked the company about this, their explanation was that patients included in trial 1205 had a longer time from start of symptoms until presentation for treatment.

Open follow-up study: study 1304 OLE
During the open follow-up period (6 months), 33 patients with HAE were treated for a total of 70 acute angioedema attacks with an initial dose of RUCONEST 2100 U. Median times to relief of symptoms (improvement in VAS score) are summarised in the table below:

	1st attack (N=36)	**2nd attack (N=17)**	**3rd attack (N=8)**	**4th attack (N=3)**	**5th attack (N=2)**
median time to symptom relief (minutes) (95% CI)	60 [34; 120]	60 [31; 121]	120 [20; 719]	62 [32; 958]	46 [31; 61]

The study appears to show that the efficacy of RUCONEST is maintained. These results should be interpreted with caution in view of the small number of patients followed-up.

3.2. Adverse effects

In trial 1205, 15 patients (39%) experienced adverse events (4 in the RUCONEST 50 U/kg group, 5 in the RUCONEST 100 U/kg group and 6 in the placebo group). The most common adverse events were:

- headache: 0 vs. 2 vs.1,
- skin disorders (erythema, pruritus, rash): 2 vs. 0 vs. 0,
- acute renal failure: 0 vs. 1 vs. 0.

In trial 1304, 10 patients (31%) experienced adverse events (2 in the RUCONEST group and 8 in the placebo group).
The most common adverse events were:

- abdominal pain: 1 vs. 2,
- reproductive system disorders (menstrual disorders and swelling of the scrotum): 2 vs. 0,
- headache: 1 vs. 3.

According to the SPC, "The clinical experience supporting the tolerance of RUCONEST consists of 300 administrations (83 administrations to healthy subjects or asymptomatic HAE patients and 217 administrations to 119 HAE patients). The most commonly reported adverse event (>1%) was headache".

3.3. Immunogenicity

The active ingredient of RUCONEST, conestat alfa, is a recombinant analogue of the human C1 esterase inhibitor (rhC1INH) produced by recombinant DNA technology in the milk of transgenic rabbits. It contains traces of rabbit proteins.

Before initiating treatment with RUCONEST, patients should be tested for the presence of IgE antibodies against rabbit allergens. Only patients who have been shown to have negative results for such a test should be treated with RUCONEST. IgE antibody testing should be repeated once a year or after 10 treatments.

As with any intravenously administered recombinant protein product, hypersensitivity reactions may occur. Patients should be closely monitored and carefully observed for any symptoms of hypersensitivity throughout the period of administration of the medicine.

3.4. Conclusion

The efficacy and tolerance of RUCONEST were evaluated in two randomised double-blind trials (1205 and 1304) and their open extension phases (1205 OLE and 1304 OLE) in patients with hereditary angioedema.

In trial 1205, after one injection, there was a significant reduction in median time to relief of symptoms with RUCONEST 50 and 100 U/kg compared with placebo: 122 minutes [72 –

136] for RUCONEST 50 U/kg, 68 minutes [62 – 132] for RUCONEST 100 U/kg versus 258 minutes [240 – 495] for placebo, p=0.001.

In trial 1304, after one injection, there was a significant reduction in median time to relief of symptoms with RUCONEST 100 U/kg compared with placebo: 61.5 minutes [40-75] for RUCONEST 100 U/kg versus 508 minutes [70 -720] for placebo, p=0.003.

Time to relief of symptoms with placebo was significantly longer in trial 1304 than in trial 1205; when the EMA asked the company about this, their explanation was that patients included in trial 1205 had a longer time from start of symptoms until presentation for treatment.

The open follow-up studies (1205 OLE and 1304 OLE) seemed to show that the efficacy of RUCONEST is maintained up to the third attack; from the fourth attack, there were differences between the results of the two studies but the low number of patients followed-up makes it difficult to interpret the results.

These trials were carried out in small populations (total n=70) and few data relating to patients aged over 65 years are available. As the trials were placebo-controlled they did not include any patients with laryngeal oedema (severe form). The efficacy of RUCONEST in these severe forms has therefore not been established.

No studies against an active comparator, in particular icatibant (FIRAZYR) and C1 esterase inhibitor (human) (BERINERT) are currently available.

RUCONEST (conestat alfa) is a recombinant analogue of C1 esterase inhibitor (human) (rhC1INH) produced from the milk of transgenic rabbits. Before initiating treatment with RUCONEST, patients should be tested for the presence of IgE antibodies against rabbit allergens. Only patients who have been shown to have negative results for such a test, should be treated with RUCONEST. IgE antibody testing should be repeated once a year or after 10 treatments.

The most commonly observed adverse events during these trials (>1%) were: headache, abdominal pain, reproductive system disorders (menstrual disorders and swelling of the scrotum), and skin disorders (erythema, pruritus, rash).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hereditary angioedema (HAE) is characterised by transient and recurrent episodes of subcutaneous and/or submucosal oedema, affecting various systems (skin, gastrointestinal tract, pharynx, etc.). HAE is a rare chronic genetic disease which is incapacitating and may be life-threatening when it affects the larynx.

This proprietary medicinal product is used as symptomatic therapy;

RUCONEST is a first-line therapy.

Alternative medicinal products exist, notably BERINERT and FIRAZYR.

The efficacy/adverse effects ratio for this proprietary medicinal product is substantial.

> *Public health benefit:*
> The burden to public health of patients with acute attacks of HAE (and with a C1 esterase inhibitor deficiency) is small because few patients are involved.
> Improving the treatment of this disease is a public health need that was included in the French national rare diseases plan for 2010-2014.
> From the results of clinical trials it is not expected that the proprietary medicinal product RUCONEST would have any impact in population terms on morbidity, mortality or quality of life in these patients.
> RUCONEST does not contribute any additional response to the identified need, particularly as, like FIRAZYR and BERINERT, the product cannot be self-administered by the patient, and as it is apparently not available for use in an emergency as it can only be used in patients who have previously had a negative antibody test.
> Consequently, in the current state of knowledge, RUCONEST is not expected to have any public health benefit in this indication.

The actual benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB):

In adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency, RUCONEST does not provide any improvement in actual benefit (IAB V) compared with the other treatments available for acute HAE attacks (FIRAZYR, BERINERT).

4.3. Therapeutic use[2] [3]

HAE is characterised by episodes of subcutaneous and/or submucosal oedema, which are transient (48-72 hours) and recurrent. The disease may manifest at any age, but most commonly it appears during childhood and adolescence.

Oedema may affect the gastrointestinal tract and may lead to intestinal pseudo-obstruction, causing significant pain, sometimes combined with ascites and low blood volume. When the larynx is affected the disease may be life-threatening.

Type I and type II HAE are caused by different alterations of the C1 esterase inhibitor (C1-INH) gene, i.e. deletion or poor transcription for type I and mutation for type II. Diagnosis of type I and type II HAE is based on determination of C4 concentration and determination of

2 Dr L. Bouillet "Angio-œdème héréditaire [Hereditary angioedema]", Orphanet, February 2008.
3 EPAR summary for FIRAZYR – 24 April 2008

C1-INH. Oedema is triggered by increased blood vessel permeability caused by excessive bradykinin release due to the C1-INH inhibitor deficit.
Current treatment consists of prophylactic therapy to prevent attacks, avoidance of identifiable trigger factors (foods, medicines such as CEI inhibitors, etc.) and short-term treatment of attacks. Corticosteroids are not effective.

- prophylactic therapy is an androgen (danazol),
- treatment for moderate attacks is tranexamic acid (EXACYL, off-label); treatment of severe attacks (laryngeal) is intravenous administration of concentrated C1-INH (BERINERT) or subcutaneous administration of icatibant (FIRAZYR).

RUCONEST has demonstrated its efficacy in terms of median time to relief of symptoms in HAE attacks and is an alternative to the other available therapies for HAE attacks (FIRAZYR, BERINERT).

4.4. Target population

The target population for RUCONEST is patients with acute attacks of hereditary angioedema (HAE) and a C1 esterase inhibitor deficiency, who have no IgE antibodies against rabbit allergens.

The population can be estimated on the basis of the following data:

- according to the French reference centre for non-histamine-induced angioedema,[4] 1000 patients had hereditary angioedema in 2007,
- 85% of these patients are thought to have a C1 esterase deficiency,
- the proportion of patients with IgE antibodies against rabbit allergens or likely to develop them is not known.

In view of the very limited nature of the epidemiological data available concerning forms which could be treated with RUCONEST, the target population cannot be estimated with any certainty. However, the data described above and the opinion of experts make it possible to estimate the number of patients having attacks of hereditary angioedema with C1 esterase deficiency as about 650 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicinal products approved for hospital use and various public services in the indication in the Marketing Authorisation.

[4] CREAK "les angio-oedèmes non histaminiques" [non-histamine-induced angioedema] L. Bouillet, 01 July 2007.