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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on an extension of Marketing Authorisation

Ruconest

International non-proprietary name: conestat alfa

Procedure No. EMEA/H/C/001223/X/0034



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1. Background information on the procedure

1.1. Submission of the dossier

Pharming Group N.V submitted on 11 January 2016 an extension of the marketing authorisation.

The MAH proposed the addition of a new pharmaceutical form "powder and solvent for solution for injection".

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0004/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0004/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.2. Steps taken for the assessment of the product

The Rapporteur and PRAC Rapporteur appointed by the CHMP were:

Rapporteur: Nithyanandan Nagercoil Co-Rapporteur: N/A

PRAC Rapporteur: Rafe Suvarna

CHMP Peer reviewer(s): N/A

- The application was received by the EMA on 11 January 2016.
- The procedure started on 28 January 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016 (Annex 1).
- During the meeting on 23-26 May 2016, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 26 May 2016 (Annex 2).

- The MAH submitted the responses to the CHMP consolidated List of Questions on 18 July 2016.
- The PRAC Rapporteurs circulated the PRAC Rapporteur Assessment Report on the responses to the List of Questions to all PRAC and CHMP members on 17 August 2016 (Annex 3).
- The Rapporteurs circulated the Assessment Report on the responses to the List of Questions to all CHMP members on 8 September 2016 (Annex 4).
- During the PRAC meeting on 30 August-2 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the MAH on 2 September 2016 (Annex 5).
- During the CHMP meeting on 12-15 September 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the MAH (Annex 6).
- MAH submitted the responses to the CHMP List of Outstanding Issues on 11 October 2016.
- The PRAC Rapporteurs circulated the PRAC Rapporteur Assessment Report on the responses to the List of outstanding issues to all PRAC and CHMP members on 18 October 2016 (Annex 7).
- The Rapporteurs circulated the Assessment Report on the responses to the List of outstanding issues to all CHMP members on 27 October 2016 (Annex 8).
- During the PRAC meeting on 24-27 October 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the MAH on 27 October 2016 (Annex 9).
- During the meeting on 7-10 November 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Ruconest.

2. Scientific discussion

2.1. Problem statement

Ruconest (INN, conestat alfa) is the recombinant analogue of human C1 esterase inhibitor and is obtained from the milk of rabbits expressing the gene encoding for human C1 esterase inhibitor. The amino acid sequence of the recombinant form is identical to endogenous human C1 esterase inhibitor. Ruconest 2100 U is presented as a powder for solution for injection and is intended for intravenous administration.

The European Commission granted a marketing authorisation valid throughout the European Union for Ruconest 2100 U powder for solution for injection on 28 October 2010.

At present, subjects with hereditary angioedema need to attend a clinical facility to receive Ruconest 2100 U powder for solution for injection to manage an acute attack.

The MAH now seeks to add a new pharmaceutical form "powder and solvent for solution for injection" to the existing Marketing Authorization i.e. Ruconest 2100 U powder for solution for injection. The proposed presentation for the a new pharmaceutical form is a complete kit package including solvent and

administration devices and is intended to facilitate administration by the patient or the caregiver in the home care setting (home-treatment/self-administration).

The MAH seeks to add the following wording to section 4.4 of the SmPC:

Home-treatment and self-administration

There are limited data on the use of this medicinal product in home- or self administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of adverse drug reactions, particularly hypersensitivity. The decision on the use of home-treatment for an individual patient should be made by the treating physician, who should ensure that appropriate training is provided and the use reviewed at intervals.

As background, the application EMEA/H/C/001223/II/0019/G (Update of sections 4.2, 4.4 and 6.6 of the SmPC with new information on self-administration of conestat alfa during acute attacks of Hereditary Angioedema and to remove the prescribing advice on IgE testing) was withdrawn by the MAH as the CHMP considered that the authorised presentation, powder for solution for injection, if made available for self-administration would be associated with significant risk of medication errors. Indeed, it was considered that Ruconest was packaged in a form which doesn't allow for easy self-administration. The CHMP recommended that the MAH provide a solvent and administration kit to facilitate the self-administration. Further to receipt of the CHMP's recommendations, the MAH started the development of an administration kit and submitted the present application

2.1.1. Disease or condition

Hereditary angioedema is caused by a deficiency of C1 esterase inhibitor. C1 esterase inhibitor is a protease inhibitor belonging to the serpin superfamily. Its main function is the inhibition of the complement system to prevent spontaneous activation. Deficiency of C1 esterase inhibitor is associated with hereditary angioedema.

Hereditary angioedema presents as marked swelling of the face, mouth and/or airway [leading to difficulty breathing] and intestinal oedema [causing abdominal pain]. Swelling can occur in any part of the body. Episodes may occur spontaneously or in response to triggers such as trauma, medications, viral illness and stress.

2.1.2. Epidemiology

Hereditary angioedema has an estimated prevalence of (about) 1 out of 10,000. There is no known difference in prevalence across ethnic groups or gender.

2.1.3. Aetiology and pathogenesis

In its most common form, hereditary angioedema presents as marked swelling of the face, mouth and/or airway [leading to difficulty breathing] and intestinal oedema [causing abdominal pain]. Swelling can occur in any part of the body. Episodes may occur spontaneously or in response to triggers such as trauma, medications, viral illness and stress. The frequency of acute angioedema attacks varies widely but on average is approximately 4-5 times per year. Patients have reported as few as 0 and as many as 50 attacks per year.

2.1.4. Clinical presentation, diagnosis

The European Register of Hereditary Angioedema reports a median age of symptom onset of 11 years and a median age of diagnosis at 26 years.

2.1.5. Management

Other medicinal products used in the management of hereditary angioedema are registered for self-administration.

About the product

This is a licence extension application to add a new pharmaceutical form "powder and solvent for solution for injection" to the existing Marketing Authorization: Ruconest 2100 U powder and solvent for solution for injection. The new product format will be comprised of:

- One Ruconest powder vial
- One Ruconest solvent vial, containing water for injection.
- Two vial adaptors: vented vial adapter with 15 µm filter.
- One syringe 20 ml / Luer Lock
- One infusion set (winged infusion set with needle protection)
- Two alcohol pads
- One sterile non-woven pad
- One self-adhesive plaster

Type of Application and aspects on development

- Legal basis: extension application
- Accelerated procedure: n/a
- Conditional approval: n/a
- Exceptional circumstances: n/a
- Biosimilar application: n/a
- 1 year data exclusivity: n/a
- Significance of paediatric studies: n/a

2.2. Quality aspects

2.2.1. Introduction

This is an application to add a new dosage form, Ruconest 2100 U powder and solvent for solution for injection, to the existing Marketing Authorization. The proposed presentation for the additional dosage form is a complete kit package, including solvent (water for injections) and administration devices, intended to facilitate administration by the patient or the caregiver in the home care setting (home-treatment/self-administration).

2.2.2. Active Substance

There are no changes declared for the active substance part of module 3.

2.2.3. Finished Medicinal Product

The product is administered as a bolus injection. In the home setting, this will need to be performed with an administration kit. The new product format will be comprised of:

- One Ruconest powder vial
- One Ruconest solvent vial, containing water for injections.
- Two vial adaptors: vented vial adapter with 15 µm filter.
- One syringe 20 ml / Luer Lock
- One infusion set (winged infusion set with needle protection)
- Two alcohol pads
- One sterile non-woven pad
- One self-adhesive plaster

Information provided with respect the finished medicinal product has only been updated for the sterilised water for injections (WFI) and the administration devices.

Water for injections

The WFI component has been confirmed as complying with the current Ph. Eur. Monograph. The manufacturing process has been described in sufficient detail. The limits for all the in-process controls are acceptable and satisfactory validation data for three batches has been provided. A shelf life of 60 months has been demonstrated.

The WFI vial is made of colourless neutral glass, glass type I (Ph. Eur.). The nominal volume is 20 ml. The stopper is a type I stopper (Ph. Eur.). The basic polymer is chlorobutyl. The stopper is coated with FluroTec.

The integrity of the container closure system of the 20 ml vials, stoppers and caps was successfully tested by the bacterial intrusion test.

Administration devices

All administration devices are medical devices with a CE mark and are used for the purpose specified by the device manufacturer and for which they have been CE tested.

The results of compatibility studies indicate that the reconstituted product is compatible with the syringes and infusion equipment provided for a period up to 4 hours. In clinical practice reconstitution is performed by adding 14 mL WFI to each powder vial, resulting in a targeted conestat alfa (rhC1INH) concentration of 150 U/mL (= 2100 U per vial). The contact time with the application device is less than 15 minutes.

It should be noted that the in-use stability for the reconstituted product remains unchanged.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The submission provides information supportive of the new contact materials provided as part of the administration kit and the vial of sterilised water for injections intended for reconstitution.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

This extension submission is to add another product format of Ruconest which will incorporate elements to aid self-administration in the home setting. The product is approvable from a quality perspective.

2.3. Non-clinical aspects

The MAH didn't submit new non clinical data to support this application which is acceptable to the CHMP.

Recombinant human C1 inhibitor is a human protein and is similar to its natural counterpart which is available in human media. Based on the above, any potential risks for the environment are not anticipated and as such an environmental risk assessment is not required as per the CHMP guideline Environmental Risk Assessment of Medicinal Products for Human Use (CPMP1SWP14447I00). Hence, the MAH didn't submit an ERA which is acceptable to the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

Formal clinical studies on patients were not submitted as part of this application. The MAH has submitted a combined 'readability' and 'usability' study of the patient information texts for Ruconest 2100 U powder and solvent for solution for injection.

The CHMP noted that new clinical studies were not submitted to support this line extension; the clinical efficacy and safety of Ruconest have been demonstrated in the initial marketing authorisation and subsequent procedures.

In addition, the MAH has submitted a summary of known clinical safety drawn from a combination of clinical studies and post-marketing experience. Novel unfavourable effects have not been identified for Ruconest.

2.4.2. Clinical efficacy

Combined 'readability' and 'usability' study

Study title: Usability test and readability focus test of the instructions for use of Ruconest 2100 U powder and solvent for solution for injection, self-administration kit.

Date of study: pilot study: 10 to 12 November 2015; main study: 8 to 12 December 2015

Aim of study: patients and caregivers will be able to prepare and administer the Ruconest solution correctly by following the instructions in the package leaflet, particularly the instructions for use.

Objective of study: to assess whether people without a healthcare background, or prior experience in the preparation/administration of infusion medicines, can prepare and administer the Ruconest infusion within the confines of the product specific requirements. A worst case scenario will be investigated.

Risk analysis: the MAH refers to "Failure Mode and Effects Analysis" (FMEA) and FDA draft guidance "Applying Human Factors and Usability Engineering to Optimize Medical Device Design" to guide its analysis in order to identify possible risks (use-related hazards) and their causes and in order to prevent these occurring while using the Ruconest self-administration kit.

Study pre-phase:

A systematic review and optimisation of the package leaflet's instructions for use (text, layout, and illustrations) was carried with reference to published literature and to in-house experience.

A recheck of optimised instructions for use was carried out by two nurses, neither of whom had any involvement in any of the other pre-phase steps.

Revisions to study material were made on the basis of the pre-phase: changes were made to text (e.g. to simplify, use larger font and 'active' language) and layout (e.g. use of bullet points, key messages were highlighted, use uniform style of illustration), sentences were shortened (removal of repetition and 'difficult' words) and advice on how to remove bubbles was extended. The CHMP noted that a pre-phase check, as described, is acceptable.

The Ruconest self-administration kit containing two powder vials and two solvent vials ("2+2 kit") was selected for the study because this packaging size can be used by all patients irrespective of their weight and because it also represents the use of other pack sizes, such as that containing only one powder vial and one solvent vial ("1+1 kit"). The CHMP noted that use of the "2+2" kit, as described, is acceptable

Volunteer selection:

Volunteers (male and female) were randomly selected from participant pool.

- 6 volunteers (4 adults and 2 adolescents aged 14 to 18 years) were recruited for the pilot test
- 20 new volunteers (15 adults and 5 adolescents aged 14 to 18 years) were recruited for the main study.

The CHMP acknowledged that the number of participants is consistent with: Position paper on user testing of package leaflet consultation with target patient groups (compliance with article 59(3) of Council Directive 2001/83/EC), CMDh/234/2011, Feb 2011.

Pilot study

6 people took part in the pilot study. In general, test volunteers located and understood all required information with ease.

For the usability test, all volunteers performed the preparation and administration without previous training or experience in this specific topic (worst case scenario). Numerous errors were made by all subjects in both preparation of the solution and administration. The worst case scenario was considered necessary to check the instructions for use. If training were to be provided before conducting the usability test, then the quality of the training would be assessed rather than the instructions for use.

The average time of the six volunteers to perform all usability test steps was 56 minutes.

The volunteers made suggestions to improve the instructions for use (mainly text and illustration amendments); it was recommended that the size of the powder label should be reduced, or an alternative measure should be taken, so that people could more easily see whether the solution was clear and without particles.

The instructions for use were modified as a result of experience of the pilot test.

Main study

21 people were recruited.

Readability: volunteers located and understood at least 80 % of the information queried in each question concerning the content of the instructions for use. Twelve (12)/21 people did not make any error (answer not found or incorrect answer), 8/21 made one error each and 1/21 made two errors.

Useability: With the exception of "tighten the fist" in step 11c and "release the tourniquet" in step 12e in the usability test, volunteers were also able to perform properly ["√" or "(√)"] each single preparation or administration point in at least 80 % of cases.

The seven problems which occurred in "tighten the fist" and the five in "release the tourniquet" can be explained by the fact that a "dummy arm" instead of a real person was used, which cannot tighten the fist.

The shorter than recommended 3 to 5 minutes for a volume of 14 ml taken by participants to inject the prepared solution into a vein, can also be explained by the fact that the administration was carried out on a "dummy arm" instead of a real person. In addition, no timer was provided to the volunteers during the usability test to avoid any influences on the results.

Four (4)/21 subjects had given injections before either to themselves or to their children. The CHMP noted that it is noticeable that those who had experience of giving injections seem to record less problems with the technical aspects of administration.

The CHMP noted that some subjects were able to comply with instructions, some needed some guidance from the supervisor and others experienced difficulties and needed much input from the supervisor. Foaming of product during preparation appears to have been an issue.

2.4.3. Clinical safety

The MAH submitted an Integrated Summary of Safety (ISS) summarizing the clinical and selected nonclinical data relevant to the safety and tolerability of recombinant human complement component 1 (C1) esterase

inhibitor (rhC1INH; Recombinant human complement component 1 esterase inhibitor; International Nonproprietary Name: conestat alfa) used for the treatment of acute attacks of angioedema in patients with hereditary angioedema (HAE).

Analysis Data Sets

Data for patients in these studies were pooled into three analysis sets as follows: the RCT Safety Analysis Set, the Safety Analysis Set, and the Asymptomatic (Asymp)/HV Analysis Set. This pooling strategy for summarizing rhC1INH safety data was communicated to and recommended by the United States (US) Food and Drug Administration (FDA) at the pre-Biologics License Application (BLA) meeting between the Sponsor and the FDA, which occurred on 25 February 2010.

RCT Safety Analysis Set

The RCT Safety Analysis Set includes pooled safety data from Study 1205 RCT, Study 1304 RCT, and the RCT Phase of Study 1310 evaluating rhC1INH in patients with symptomatic HAE. In these studies, patients with HAE received a single treatment of rhC1INH or saline for an acute angioedema attack. All patients participating in Studies 1205 RCT, 1304 RCT, and the RCT Phase of Study 1310 who received double-blind treatment (rhC1INH or saline) are included in this set.

Overall, the RCT Safety Analysis Set is a subset of the Safety Analysis Set and includes a total of 137 unique patients who were treated for 144 angioedema attacks. Specifically, this set includes:

- 12 patients in Study 1205 RCT and 43 patients in the RCT Phase of Study 1310 who received rhC1INH 50 U/kg, including five patients who received a second dose of 50 U/kg (total of 53 unique patients [two patients each participated in both studies])
- 13 patients in Study 1205 RCT and 16 patients in Study 1304 RCT who received rhC1INH 100 U/kg (total of 29 unique patients);
- 13 patients in Study 1205 RCT, 16 patients in Study 1304 RCT, and 31 patients in the RCT Phase of Study 1310 who received saline (total of 59 unique patients [one patient participated in two studies])

In each of these studies, patients were treated for a single HAE attack. However, because the same patients could have participated in more than one study, only unique patients in each dose group are counted in the patient totals shown in the bulleted points above. Similarly, patients could be represented in more than one dose group, with only unique patients counted in the total number of patients. Therefore, the overall total number of unique patients (N=137) is less than the sum of patient totals for each dose group shown above. This consideration also explains the number of RCT-treated attacks (N=144) being greater than the total number of unique patients in the RCT Safety Analysis Set (N=137).

Safety Analysis Set

The Safety Analysis Set includes pooled safety data from Studies 1202, 1203, 1205 RCT, 1205 OLE, 1304 RCT, 1304 OLE, and 1310 (RCT and OLE Phases) evaluating rhC1INH in patients with symptomatic HAE. In the OLE studies/phase, patients with HAE could receive repeated treatments for acute angioedema attacks.

This analysis set includes all patients who received double-blind treatment (rhC1INH or saline) or open-label treatment (rhC1INH) in any of the aforementioned seven clinical studies. The Safety Analysis Set includes data for a total of 205 symptomatic patients with HAE who were treated with rhC1INH for a total of 650 acute angioedema attacks. The greatest number of treated attacks was counted for patients who received rhC1INH

50 U/kg single dose or 50 U single dose + additional dose (145 patients treated for 393 attacks), the rhC1INH dose for which licensure is sought. All safety data for the saline group in the Safety Analysis Set are derived from the RCT studies as no patients received saline in the OLE studies/phase.

Asymp/HV Analysis Set

The Asymp/HV Analysis Set is defined as the set of asymptomatic patients with HAE (Studies 1101 and 1207) and HV subjects (Study 1106) treated in clinical trials of rhC1INH. This set includes 51 subjects who received 290 doses of rhC1INH (ranging from 6.25 to 100 U/kg).

Key safety conclusions are summarized as follows:

When administered at doses of 50 or 100 U/kg, rhC1INH was safe and well tolerated in patients with HAE. The safety profile associated with repeated administrations of rhC1INH was consistent with that associated with single administrations.

No safety concerns were raised with regard to the reported TEAEs (type, frequency, severity, and/or relatedness), SAEs, TEAEs leading to study discontinuations, or TEAEs of focused clinical interest including immunogenicity, hypersensitivity reactions, and thromboembolic events.

- Overall, TEAE frequency in the saline group was comparable with those in the rhC1INH dose groups.
- Most TEAEs were assessed as mild or moderate in severity and not related to study drug.
- No deaths were reported for symptomatic HAE patients. One death assessed as unrelated to study drug was reported among asymptomatic HAE patients 25 days after receiving the final dose of rhC1INH.
- The frequency of SAEs was low regardless of the dose group. All but one SAE experienced after rhC1INH administration were considered to be unrelated to study drug. The exception was an SAE of hypersensitivity (moderate in severity) considered to be possibly related to study drug.
- No study discontinuations due to AEs were reported.
- No patients tested positive for neutralizing antibodies to pdC1INH.

Confirmed anti-C1INH and anti-HRI antibodies were observed infrequently and were not associated with clinical symptoms. There was no plausible temporal association between TEAEs or new acute HAE attacks and the presence of any confirmed anti-C1INH or anti-HRI antibodies.

- Pre-existing IgE antibodies to animal allergens did not appear to be of clinical significance except in participants with a known clinical history of rabbit allergy.
- The risk of Type I hypersensitivity is minimal in patients without clinical allergy to rabbits, and the risk of development of a hypersensitivity reaction to rhC1INH is minimal.
- An anaphylactic reaction was experienced by one HV subject with an undisclosed clinical history of rabbit allergy; other observed potential hypersensitivity reactions were not serious, typically resolving spontaneously.
- No thromboembolic events were observed.

No safety concerns arose regarding clinical laboratory findings; changes in vital sign measurements, and/or ECG recordings.

2.4.4. Conclusions on the clinical aspects

New clinical studies are not submitted to support this line extension; the clinical efficacy and safety of Ruconest have been demonstrated in the initial marketing authorisation and subsequent procedures. This is acceptable to the CHMP.

The MAH has submitted a combined 'readability / usability' study carried that involved a pilot test on 6 healthy subjects and a main test on 21 healthy subjects. The CHMP considered that the user test data is supporting data only. However, the user test submitted is performance-based, the questions asked are considered to be reasonable and the MAH sought general feedback on the overall quality of the leaflet instructions.

It would have been preferred if the MAH had analysed [from a first round of 'usability'] how subjects interacted with the giving device and had then acted upon information so-gleaned.

The 'usability' element of the user test has shown that competence is needed to self-administer. It is therefore considered to be necessary to ensure that the attending healthcare practitioners are satisfied with regards to the competence of the recipient (or care-giver) before home administration is undertaken in any one case. Hence the MAH has revised the SmPC to include advice under 'Method of Administration' to ensure that the patient is competent to administer Ruconest before home-administration is permitted.

The test has also identified that there is a need to give patients clear instructions on how to deal with foaming of the product during preparation. At the CHMP request, the SmPC states that the product must be administered by a healthcare professional until the patient (or caregiver) is competent to administer after having been properly trained and in agreement with the healthcare professional.

Of note, a statement regarding cow's milk allergy was missing from the SmPC for the powder for solution for injection and has been re-introduced.

The 'readability' element of the user test submitted is performance-based, the questions asked are considered to be reasonable and the MAH sought general feedback on the overall quality of the leaflet instructions.

The MAH has submitted a summary of known clinical safety drawn from a combination of clinical studies and post-marketing experience. Novel unfavourable effects have not been identified for Ruconest.

Thus far an anaphylactic reaction to Ruconest has only been detected in one healthy volunteer participating in a clinical trial with Ruconest. The study subject had not disclosed a history of rabbit allergy, which was an exclusion criterion in the study. A clinical history of allergy supplemented by appropriate testing should be able to detect those who may react in this manner and so avoid the situation occurring within a home setting. This risk is adequately addressed in the PI and the RMP.

To minimise the risk of medication error and/or to ensure appropriate administration of Ruconest as it is not feasible to achieve this through the product information and labelling alone, the MAH has updated the existing educational materials. These educational materials will provide adequate instruction and training for the patient and HCP on how to use Ruconest at home. Educational materials will provide information on the training to be provided to patients or caregivers before any treatment can be administered at home and will provide a diary for patients to record date and time of treatment, batch number and dose, response to treatment and any adverse events.

Home-administration will require ongoing assessment of patients' ability to take their medicines in this

manner. Hence, the MAH should submit the protocol concerning the effectiveness evaluation of additional risk minimisation measures to the EMA within 2 months of completion of this procedure.

2.4.5. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Allergic reactions in patients with rabbit allergy • Off label use • Lack of efficacy
Important potential risks	<ul style="list-style-type: none"> • Allergic reaction due to cross reaction with IgE antibodies against cow milk • Allergic reaction due to the formation of IgE antibodies against rabbit allergens • Allergic reaction due to formation of other anti-Host Related Impurities (HRI) antibodies • Induction of acquired angioedema due to the formation of antiC1INH antibodies • Thromboembolic complications • Medication error* • Adverse events with self or home administration*
Missing information	<ul style="list-style-type: none"> • Data on paediatric patients are limited • Data on pregnant and breast-feeding women are limited

The safety concerns marked with * have been added during this procedure.

Pharmacovigilance plan

Study	Objectives	Safety concerns addressed	Status	Date for submission of report
Study C1 1412; registry (clinical, 3), non-interventional	To observe adverse events and insufficient efficacy, and to assess the immunological profile following single and repeated treatment with Ruconest in patients diagnosed with HAE.	- To expand the safety database for Ruconest.	Started	Final study report 31 March 2018
Study C1 1209; paediatric study (clinical, 3), interventional	To assess: - Clinical safety, immunogenicity, and tolerability of Ruconest in HAE patients of 2-13 year old. - Pharmacokinetics (PK) and pharmacodynamics (PD) of Ruconest in these patients. - Efficacy of Ruconest in these patients.	- Data on safety and efficacy in paediatric patients are limited.	Started	Final study report 31 December 2016

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Allergic reactions in patients with rabbit allergy	<p><u>This risk is covered by the SmPC sections 4.2, 4.3 and 4.4:</u></p> <p><i>4.2 Posology and method of administration</i> <i>Ruconest should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of hereditary angioedema.</i></p> <p><i>4.3 Contraindications</i> <i>Known or suspected allergy to rabbits (see section 4.4).</i></p> <p><i>4.4 Special warnings and precautions for use</i> <i>Conestat alfa is derived from milk of transgenic rabbits and contains traces of rabbit protein. Before initiating</i></p>	Educational materials for physicians and patients.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p><i>treatment with Ruconest, patients should be queried about prior exposure to rabbits and signs and symptoms suggestive of an allergic reaction indicative of a rabbit allergy.. Hypersensitivity reactions cannot be excluded. Patients must be closely monitored and carefully observed for any symptoms of hypersensitivity throughout 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.</i></p> <p><u>Other routine risk minimisation measures:</u> Prescription only medicine.</p>	
Off label use	<p><u>Other routine risk minimisation measures:</u> Prescription only medicine.</p>	Not applicable.
Lack of efficacy	<p><u>This risk is covered by the SmPC section 4.2:</u></p> <p><i>In the majority of cases a single dose of Ruconest is sufficient to treat an acute angioedema attack. In case of an insufficient response, an additional dose (50 U/kg weight up to 4200 U) can be administered (see section 5.1). Not more than two doses should be administered within 24 hours.</i></p> <p><u>Other routine risk minimisation measures:</u> Prescription only medicine.</p>	Not applicable.
Allergic reaction due to cross reaction with IgE antibodies against cow milk	<p><u>This potential risk is covered by the SmPC section 4.4.</u></p> <p><i>4.4 Special warnings and precautions for use</i> <i>Conestat alfa is derived from milk of transgenic rabbits and contains traces of</i></p>	Educational materials for physicians and patients.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p><i>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 towards rabbits.</i></p> <p><i>Hypersensitivity reactions cannot be excluded. Patients must be closely monitored and carefully observed for any symptoms of hypersensitivity throughout 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.</i></p> <p><i>In case of anaphylactic reactions or shock, emergency medical treatment should be administered.</i></p> <p><i>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. Patients with cow's milk allergy should be informed that they might react to Ruconest. A skin prick test can be performed to exclude cross-reactivity between cow milk and rabbit milk.</i></p> <p><u>Other routine risk minimisation measures:</u> Prescription only medicine.</p>	
Allergic reaction due to the formation of IgE antibodies against rabbit allergens	<p><u>This potential risk is covered by the SmPC section 4.4:</u></p> <p><i>4.4 Special warnings and precautions for use</i></p> <p><i>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</i></p>	Educational materials for physicians and patients.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p><i>rabbits and signs and symptoms suggestive of an allergic reaction towards rabbits.</i></p> <p><i>Hypersensitivity reactions cannot be excluded. Patients must be closely monitored and carefully observed for any symptoms of hypersensitivity throughout 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.</i></p> <p><i>In case of anaphylactic reactions or shock, emergency medical treatment should be administered.</i></p> <p><u>Other routine risk minimisation measures:</u></p> <p>Prescription only medicine.</p>	
Allergic reaction due to formation of other anti-Host Related Impurities (HRI) antibodies	<p><u>Other routine risk minimisation measures:</u></p> <p>Prescription only medicine.</p>	<p>Educational materials for physicians and patients.</p> <p>The company has made available anti-HRI antibody tests for any HAE patients meeting any of the following criteria:</p> <p>Type III hypersensitivity reaction (skin, joints or kidney symptoms) in temporal relation with a Ruconest administration which after investigation of other causes cannot be explained by exposure and reaction to other allergens;</p> <p>Type III hypersensitivity reactions in temporal relation with two consecutive administrations of Ruconest.</p> <p>For HAE patients meeting at least one of these two criteria, the following immunogenicity testing panels will be made available.</p> <p>1) Anti-HRI_{SP-eluate} antibody testing (total Ig). In the event that above cut-off values are observed in the anti-HRI_{SP-eluate} test, a confirmatory displacement</p>

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		<p>test is performed on the sample.</p> <p>2) Anti-rhC1INH antibody testing (IgG and IgM). In the event that above cut-off values are observed in either anti-rhC1INH antibody test, a confirmatory displacement test is performed on the sample. In the event of a positive displacement test, the sample is tested for neutralizing antibodies to pdC1INH.</p>
Induction of acquired angioedema due to the formation of anti-C1INH antibodies	Not applicable.	<p>Educational materials for physicians and patients. The company has made available anti-C1INH antibody tests for any HAE patients meeting any of the following criteria:</p> <ol style="list-style-type: none"> 1) In two consecutive acute angioedema attacks there is a need for a dose greater than 50 U/kg rhC1INH in any HAE patient that previously responded to treatment with 50 U/kg rhC1INH. 2) In two consecutive acute angioedema attacks a failure to respond to rhC1INH treatment within 4 hours despite adequate dosing of 50 U/kg in any HAE patient who previously responded to treatment with 50 U/kg rhC1INH. <p>For HAE patients meeting at least one of these two criteria, the following immunogenicity testing panel will be recommended and made available:</p> <p>Measure functional C1INH activity 15 minutes after infusion of adequate dose of Ruconest. If C_{max} does not achieve at least 0.7 U/mL: Anti-rhC1INH antibody testing (IgG and IgM). In the</p>

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		event that above cut-off values are observed in either anti-rhC1INH antibody test, a confirmatory displacement test is performed on the sample. In the event of a positive displacement test, the sample will be tested for neutralizing antibodies to pdC1INH.
Thromboembolic complications	<u>Other routine risk minimisation measures:</u> Prescription only medicine.	Not applicable.
Medication error	<u>Other routine risk minimisation measures:</u> Prescription only medicine.	Educational materials for physicians and patients.
Adverse event with self or home administration	<u>Other routine risk minimisation measures:</u> Prescription only medicine.	Educational materials for physicians and patients.

In line with the revised Annex II requirements, educational materials should include information on the training to be provided to patients or caregivers before any treatment can be administered at home and should provide a diary for patients to record date and time of treatment, batch number and dose, response to treatment and any adverse events.

The MAH should submit the protocol concerning the effectiveness evaluation of additional risk minimisation measures to the EMA within 2 months of completion of this procedure.

Conclusion

The PRAC and CHMP considered that the risk management plan version 16 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hereditary angioedema has an estimated prevalence of (about) 1 out of 10,000. There is no known difference in prevalence across ethnic groups or gender. The European Register of Hereditary Angioedema reports a median age of symptom onset of 11 years and a median age of diagnosis at 26 years.

Hereditary angioedema is caused by a deficiency of C1 esterase inhibitor; C1 esterase inhibitor inhibits the complement system to prevent spontaneous activation. Ruconest (conestat alfa) is a recombinant human C1 esterase inhibitor that is administered by intravenous injection.

Hereditary angioedema presents as marked swelling of the face, mouth and/or airway [leading to difficulty breathing] and intestinal oedema [causing abdominal pain]. Swelling can occur in any part of the body. Episodes may occur spontaneously or in response to triggers such as trauma, medications, viral illness and stress. The frequency of acute angioedema attacks varies widely but on average is approximately 4-5 times per year. Patients have reported as few as 0 and as many as 50 attacks per year.

3.1.2. Available therapies and unmet medical need

Other medicinal products used in the management of hereditary angioedema are registered to be administered at home.

However, subjects with hereditary angioedema need to attend a clinical facility to receive Ruconest to manage an acute attack. Hence, the MAH now seeks to add a new pharmaceutical form "powder and solvent for solution for injection" to the existing Marketing Authorization i.e. Ruconest 2100 U powder and solvent for solution for injection. The proposed presentation for the additional pharmaceutical form "powder and solvent for solution for injection" is a complete kit package including solvent and administration devices and is intended to facilitate administration by the patient or the caregiver in the home care setting (home-treatment/self-administration).

3.1.3. Main clinical studies

New clinical studies are not submitted to support this line extension; the clinical efficacy and safety of Ruconest have been demonstrated in the initial marketing authorisation and subsequent procedures.

The MAH has submitted a combined 'readability / usability' study carried that involved a pilot test on 6 healthy subjects and a main test on 21 healthy subjects. The CHMP considered that the user test data is considered as supporting data only. However, the user test submitted is performance-based, the questions asked are considered to be reasonable and the MAH sought general feedback on the overall quality of the leaflet instructions.

3.2. Favourable effects

New clinical studies are not submitted to support this line extension; however, the clinical efficacy and safety of Ruconest have been demonstrated in the initial marketing authorisation and subsequent procedures.

The morbidity and mortality of hereditary angioedema may be reduced by prompt access to treatment such as by self-administration of product.

Literature published by clinical experts in the management of hereditary angioedema suggests that patients with hereditary angioedema who are willing and able to self-administer should be offered this treatment option so that attacks of acute angioedema may be treated early in their course and so reduce morbidity and mortality.

3.3. Uncertainties and limitations about favourable effects

The MAH has submitted a combined 'readability / usability' study. It is not established, however, how this experience will translate to real-world use; formal clinical studies on outcome of self-administration have not been done.

Not all subjects are competent in home-administration; such an assessment of competence will need to be done by the attending healthcare professionals. There is not a formal tool to assess competence; instead, competence will depend on various factors such as clinical experience, ability to teach and the ability of the subject to comply with instructions.

To minimise the risk of medication error and/or to ensure appropriate administration of Ruconest, the MAH has updated the existing educational materials. These educational materials will provide adequate instruction and training for the patient and HCP on how to use Ruconest at home. Educational materials will provide information on the training to be provided to patients or caregivers before any treatment can be administered at home and will provide a diary for patients.

3.4. Unfavourable effects

The combined 'readability / usability' study confirms that competence is needed in order to self-administer. Subjects who lack competence must not be allowed to administer at home. The test has also identified that there is a need to give patients clear instructions on how to deal with foaming of the product during preparation. At the CHMP request, the SmPC states that the product must be administered by a healthcare professional until the patient (or caregiver) is competent to administer after having been properly trained and in agreement with the healthcare professional.

The MAH has submitted a summary of known clinical safety drawn from a combination of clinical studies and post-marketing experience. Novel unfavourable effects have not been identified for Ruconest.

Subjects who develop anaphylactic reactions to the current product may not have quick access to treatment when administration is done at home.

If there is failure of administration at home then the time taken to fail-to-administer [about 40 to 50mins] will inevitably lead to delay in transfer to a clinical facility for rescue.

3.5. Uncertainties and limitations about unfavourable effects

The overall frequency with which anaphylactic reactions to the current product take place is unknown because the condition is too rare to permit meaningful quantification.

The consequences of delay in transfer to a clinical facility for rescue following technical failure-to-administer at home are unknown.

There are not any formal clinical studies of consequence of transfer to home-administration.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

It is considered to be very important for subjects with hereditary angioedema to be treated promptly for an acute attack in order to reduce morbidity and mortality. For this reason, home administration of Ruconest is considered to be an important component of the overall management.

Thus far an anaphylactic reaction to Ruconest has only been detected in one healthy volunteer participating in a clinical trial with Ruconest. The study subject had not disclosed a history of rabbit allergy, which was an exclusion criterion in the study. A clinical history of allergy supplemented by appropriate testing should be able to detect those who may react in this manner and so avoid the situation occurring within a home setting. This risk is adequately addressed in the PI and the RMP.

Safe use of the product has been enhanced with clear instructions in the PI e.g. on what to do if foaming occurs during preparation of the product. In addition, at the CHMP request, the SmPC states that the product must be administered by a healthcare professional until the patient (or caregiver) is competent to administer after having been properly trained and in agreement with the healthcare professional.

It is anticipated that the inability to administer because of lack of competence will be detected by attending healthcare professionals who may then continue to advice on admission to a local health facility to treat an acute attack of angioedema.

Patient competence is an important component of the appropriateness of self-medication. For this reason, educational material for both the patient and healthcare professionals is considered to be an important component of the transfer to home administration and the Annex II has been updated accordingly.

3.6.2. Balance of benefits and risks

The benefits of the ability to treat acute attacks of hereditary angioedema promptly in a home setting outweigh risks associated with such treatment.

3.6.3. Additional considerations on the benefit-risk balance

It is recognised that physicians and patients advocate management of acute attacks of hereditary angioedema in a home setting. It is also recognised that other products available for the management of acute attacks of hereditary angioedema may be administered in a home setting.

The ability to self-administer will empower the patient in his / her own management.

It may be anticipated that the ability to self-administer will lead to a reduction in morbidity and mortality associated with hereditary angioedema.

Safe use of the product has been enhanced with clear instructions in the PI e.g. on what to do if foaming occurs during preparation of the product. In addition, at the CHMP request, the SmPC states that the product must be administered by a healthcare professional until the patient (or caregiver) is competent to administer after having been properly trained and in agreement with the healthcare professional.

To minimise the risk of medication error and/or to ensure appropriate administration of Ruconest, the MAH has updated the existing educational materials. These educational materials will provide adequate instruction and training for the patient and HCP on how to use Ruconest at home. Educational materials will provide information on the training to be provided to patients or caregivers before any treatment can be administered at home and will provide a diary for patients.

3.7. Conclusions

The overall B/R of Ruconest 2100 U powder and solvent for solution for injection is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ruconest is not similar to Firazyr within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality and efficacy, the CHMP considers **by consensus** that the risk-benefit balance of, Ruconest is favourable in the following indication:

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

The CHMP therefore recommends the extension of the marketing authorisation for Ruconest subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of the product in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the National Competent Authority (NCA).

The MAH should ensure that, at launch, all Healthcare Professionals who are expected to prescribe Ruconest are provided with an educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet for Ruconest
- Educational material for the Healthcare Professional.
- Educational material for non-Healthcare Professionals.
- Diary to be given to patients before they receive Ruconest.
- Copies of the patient card to be given to patients before they receive Ruconest.

The educational material for the Healthcare Professional should include information on the following key elements:

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

- That patients treated with Ruconest should be monitored for clinical signs and symptoms of hypersensitivity during administration. Emergency medical treatment should be available immediately to be administered in case of anaphylactic reactions or shock.
- The fact that Ruconest is derived from milk of transgenic rabbits and contains trace of rabbit proteins (Host Related Impurities, HRI).
- That Ruconest is contra indicated in all patients with known or suspected rabbit allergy.
- That patients with clinical evidence of cow's milk allergy may have antibodies cross reacting with the rabbit milk impurities in Ruconest.

A protocol for performing a skin prick test (SPT) with Ruconest and an intravenous test dosing schedule in patients with a negative skin prick test, including criteria for interpreting results, for patients with clinical features of cow's milk allergy.

- The need to inform patients about the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis, and that they should alert their physician if these symptoms occur.
- The potential risk of an immune complex-mediated type III hypersensitivity reaction due to the formation of antibodies directed against Host Related Impurities (HRI). Advice about the immunogenicity laboratory testing program for detecting these antibodies for following up suspected immune complex-mediated disease, and about the procedure to follow for the collection and shipment of a blood sample to the company's central laboratory. This testing should be provided free of charge.
- The risk of formation of anti-C1INH antibodies and therefore the potential risk of formation of neutralising antibodies. Advice about the immunogenicity laboratory testing program for these antibodies provided by the company for following up suspected emergence of neutralising antibodies and information about the procedure to follow for the collection and shipment of a blood sample to the company's central laboratory. This testing should be provided free of charge.
- There are limited data on the use of this medicinal product in home or self-administration.
- The decision on the use of home treatment for an individual patient should be made by the treating physician.
- Use of Ruconest is only approved in acute attacks of hereditary angioedema.
- It is the responsibility of the physician to provide the patient or a caregiver with instructions and training on administration outside of a clinic setting.
- The training to be provided should address the following elements
 - Precaution for storage
 - Dose calculation and indication (i.e. only acute HAE attacks)
 - Preparation of one dose of Ruconest (50 U/kg, up to 4200 U) by reconstituting one or two vials
 - Method of reconstitution of each powder vial
 - Technique of intravenous injection
 - Guidance on use of a second dose of Ruconest

- Instruction to immediately seek medical attention in case of failure to gain venous access, in case of lack of efficacy, in the event of any adverse reaction including hypersensitivity, or after self-administering Ruconest for an acute laryngeal HAE attack.
- Instruction in handling possible adverse drug reactions including an acute hypersensitivity reaction
- Information on the need to keep a diary to document each treatment administered at home and to bring it at each visit. The information recorded should include:
 - Date and time of treatment
 - Batch number and dose
 - Response to treatment
 - Any adverse events
- It is the responsibility of the physician to verify that all the necessary skills have been acquired by the non-Healthcare Professional and that Ruconest may be safely and effectively administered outside of a Healthcare Professional setting.
- The existence of a post marketing registry in which healthcare professionals are encouraged to enter patients.

The educational material for non-Healthcare Professionals should include information on the following key elements:

- There are limited data on the use of this medicinal product in home or self-administration.
- For some patients the physician may decide that Ruconest may be administered outside of a clinic setting by a non-Healthcare Professional such as a family member or by self-administration.
- Use of Ruconest is only approved in acute attacks of hereditary angioedema.
- Necessary skills have to be acquired by non-Healthcare Professionals before Ruconest may be safely and effectively administered outside of a Healthcare Professional setting.
- A physician will provide training on the following elements:
 - Precaution for storage
 - Dose calculation and indication (i.e. only acute HAE attacks)
 - Preparation of one dose of Ruconest (50 U/kg, up to 4200 U) by reconstituting one or two vials
 - Method of reconstitution of each powder vial
 - Technique of intravenous injection
 - Method and rate of administration of one dose of Ruconest
 - Guidance on use of a second dose of Ruconest
- Instruction to immediately seek medical attention in case of failure to gain venous access, in case of lack of efficacy, in the event of any adverse reaction including hypersensitivity, or after self-administering Ruconest for an acute laryngeal HAE attack.
- Information on the need to keep a diary to document each treatment administered at home and to

bring it at each visit. The information collected should include:

- Date and time of treatment
- Batch number and dose
- Response to treatment
- Any adverse events

The patient diary should contain the following key elements:

- Date and time of treatment
- Batch number and dose
- Response to treatment
- Any adverse events

The patient card should contain the following key elements:

- That they are receiving Ruconest for treatment of acute attack of hereditary angioedema.
- That Ruconest is derived from milk of transgenic rabbits and contains trace of rabbit proteins.
- The importance of monitoring for clinical signs and symptoms of hypersensitivity and that patients should immediately seek medical care if they develop such symptoms during or after receiving Ruconest.
- That they should be asked to carry the card and always show it to any Healthcare Professional treating them for acute attacks of hereditary angioedema.