Part VI: Summary of the risk management plan

Summary of risk management plan for Ruconest (conestat alfa)

This is a summary of the risk management plan (RMP) for Ruconest. The RMP details important risks of Ruconest, how these risks can be minimized, and how more information will be obtained about Ruconest's risks and uncertainties (missing information).

Ruconest's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ruconest should be used.

This summary of the RMP for Ruconest should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ruconest's RMP.

I. The medicine and what it is used for

Ruconest is authorized for treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema (HAE) (see SmPC for the full indication). It contains conestat alfa as the active substance and it is given by intravenous injection.

Further information about the evaluation of Ruconest's benefits can be found in Ruconest's EPAR, including a plain-language summary, available on the EMA website, under the medicine's webpage (see https://www.ema.europa.eu/en/medicines/human/EPAR/ruconest).

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Ruconest, together with measures to minimize such risks and the proposed studies for learning more about Ruconest's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size – the amount of medicine in a pack is chosen to ensure that the medicine is used correctly.
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription).

Together, these measures constitute *routine risk minimization measures*.

In the case of Ruconest, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ruconest is not yet available, it is listed under

'missing information' below.

II.A List of important risks and missing information

Important risks of Ruconest are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ruconest. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Following completion of Study C1 1209 in children, the text on pediatric patients, classified as missing information in the list of safety has been adapted.

List of important risks and missing information	
Important identified risks	Allergic reactions in patients with rabbit allergy
	Off-label use
	Lack of efficacy
Important potential risks	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 anti-C1-INH antibodies
	Thromboembolic complications
	Medication error
	Adverse event with self or home administration
Missing information	Data on pediatric patients aged 2 up to 5 years
	Data on pregnant and breastfeeding women

II.B Summary of important risks

Important identified risk – Allergic reactions in patients with rabbit allergy	
Evidence for linking the risk to the medicine	This important identified risk is based on data from the clinical development program of conestat alfa, literature on rabbit allergy, as well as post-marketing data. The only major risk identified during the clinical development of conestat alfa has been hypersensitivity to the product, and this is based on a single serious adverse event (SAE). A healthy volunteer treated in a Phase I study developed an IgE-mediated anaphylactic event within minutes of her first dose of conestat alfa 100 U/kg. Although this subject had denied allergy to rabbits at study entry, she later reported a history of allergic symptoms upon exposure to rabbits. During and following the event, blood samples for diagnostic immunology/allergy purposes were collected, and IgE measurements were strongly positive (3+ or 4+) for

Important identified risk – Allergic reactions in patients with rabbit allergy	
	rabbit antigens. Skin testing to the study drug was positive. Of note, no anaphylactic AEs were reported in any patient with HAE who participated in the completed clinical studies of the clinical development program (acute attack and prophylactic treatment studies). A retrospective immunogenicity analysis found that single and repeat exposure to conestat alfa did not induce detectable IgE antibody responses against rabbit or other animal allergens. In a prospective analysis in Study C1 1310, no patients developed IgE antibodies to rabbit dander following treatment with conestat alfa. Rabbit allergy is contraindicated for the use of Ruconest, as indicated in the SmPC and PL. Up to the DLP of 28 October 2018, an estimated 1534 patients were exposed to Ruconest in all countries where Ruconest was approved, excluding the US. There have been no severe or serious allergic reactions (e.g. anaphylactic reaction/shock) in patients with rabbit allergy in these countries. In the US, up to the DLP of 28 October 2018, 864 patients were exposed to Ruconest. There have been no severe or serious allergic reactions (e.g. anaphylactic reaction/shock) in patients with rabbit allergy in the US, despite the lack of any pre-exposure testing requirement in the US.
Risk factors and risk groups	Rabbit allergies are more prevalent in populations with occupational exposure (e.g. laboratory animal caretakers) or in households with pet rabbits.
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.2, 4.3 and 4.4* • *PL section 2* Additional risk minimization measures: • *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Important identified risk – Off-label use	
Evidence for linking the risk to the medicine	This important identified risk is based on post-marketing data and literature. Review of the available post-marketing reports showed that reported off-label use included prophylactic use or use of Ruconest in a higher frequency than pro re nata (PRN; as needed) ranging from twice daily to every 2 weeks, off-label indications such as treatment of AAE, HAE type III, deficiencies of circulating enzymes/defects in the complement system, intramuscular administration, and use of frozen product etc. A frequency cannot be determined because it is difficult to calculate the patient exposure accurately. The reported (S)AEs associated with off-label use did not constitute any new safety signal or concern.

Important identified risk – Off-label use	
Risk factors and risk groups	The patient group which is most likely to experience limited efficacy upon use of Ruconest would be patients with AAE. These patients have neutralizing antibodies against C1-INH that are likely to also neutralize the therapeutic effect of the recombinant human C1-INH in Ruconest. In addition, prophylactic use of Ruconest could result in breakthrough attacks. Breakthrough attacks can be treated using the approved products for treatment of HAE attacks.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.1 and 4.2* *PL: section 1 and 3* Additional risk minimization measures: *Not applicable*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Important identified risk – Lack of efficacy	
Evidence for linking the risk to the medicine	This risk is based on data from clinical trials and post-marketing data on lack of efficacy. In the clinical trials, lack of efficacy was concluded if the 'time to beginning of relief' was longer than 4 hours. In the randomized controlled trials (Studies C1 1205 and C1 1304) 39/41 (95%) of patients treated with Ruconest reached time to beginning of relief within 4 hours. In an open-label study (Study C1 1205 OLE) 114/119 (95%) attacks treated with a single dose of 50 U/kg reached time to beginning of relief within 4 hours. In a subsequent randomized controlled trial (Study C1 1310 RCT), there were 35/44 (80%) of patients who achieved relief within 4 hours. In the open-label study (Study C1 1205 OLE), an additional dose of 50 U/kg was administered for 13/133 (10%) attacks. In a subsequent open-label study (Study C1 1310 OLE), a second dose was administered for 9 of 224 (4%) attacks. Based on the small patient numbers in the presented studies, lack of efficacy was observed in 5-20% of treatments in these studies and need for a second dose is estimated at 4-10% of attacks. Review of the available post-marketing data showed that the occurrence of lack of efficacy was well within the range observed in the clinical studies. Although it is hard to distinguish between lack of drug effect and worsening of the disease, due to the known mortality in HAE and specifically the possibility of severe clinical consequences of an acute angioedema attack in the laryngeal region, lack of efficacy is classified as an important identified risk.

Important identified risk – Lack of efficacy	
Risk factors and risk groups	The risk of lack of efficacy is increased in certain off-label indications such as AAE. When the product is not administered by an HCP there is an increased risk of incorrect dose used or incorrect administration of Ruconest which might result in reduced efficacy of Ruconest.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2* *PL section 3* Additional risk minimization measures: *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk – Allergic reaction due to the formation of IgE antibodies against rabbit allergens	
Evidence for linking the risk to the medicine	This risk is based on literature on rabbit allergy, data from post-marketing exposure and an IgE testing report. A post-hoc analysis of 137 subjects participating in the clinical trials revealed 2 subjects who had above threshold IgE antibodies against rabbit allergens post treatment. One of these subjects received saline in the randomized controlled phase of the study. Levels did not increase upon exposure to Ruconest in the open-label phase. The second subject had IgE antibodies against rabbit meat. Only for this patient the induction of IgE antibodies against this rabbit allergen cannot be excluded. However, the subject did not develop an allergic type response upon first or repeat exposure to Ruconest. It was concluded in the IgE testing report that single and repeat exposure to up to 100 U/ kg body weight conestat alfa did not induce detectable IgE antibody responses against rabbit or other animal allergens.
Risk factors and risk groups	Risk groups or risk factors have not been identified.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.4* *PL section 4* Additional risk minimization measures: *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk – Allergic reaction due to formation of other anti-Host Related Impurities (HRI) antibodies	
Evidence for linking the risk to the medicine	This risk is based on the immunogenicity testing report. Antibodies against HRI were assessed in samples collected from 205 HAE patients treated for 704 angioedema attacks participating in clinical Studies C1 1202 and C1 1203, and the randomized controlled (RCT) and open-label extension (OLE) parts of Studies C1 1304 and C1 1310. Anti-HRI antibody results were confirmed by displacement assay for 27 of 205 patients treated with conestat alfa. Anti-HRI antibodies were not associated with clinical symptoms. There was no plausible temporal association between treatment-emergent adverse events (TEAEs) or new acute HAE attacks and timing of any confirmed anti-HRI antibody results. In Study C1 1106, 8 out of the 11 healthy volunteers receiving 5 repeat injections of 100 U/kg had positive samples in the screenings assay for anti-HRI. In the absence of clinical symptoms, a frequency cannot be determined. The background incidence or prevalence is unknown.
Risk factors and risk groups	Risk groups or risk factors have not been identified.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.4* *PL section 4* Additional risk minimization measures: *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk – Induction of acquired angioedema due to the formation of anti-C1-INH antibodies	
Evidence for linking the risk to the medicine	This risk is based on the immunogenicity testing report. There is a theoretical risk that patients develop antibodies against conestat alfa affecting the efficacy of Ruconest, so called neutralizing antibodies. Pharming has evaluated the formation of antibodies against conestat alfa and plasma-derived C1-INH after single and repeat administrations, analyzed pharmacokinetics (PK) of C1-INH activity after repeat administrations of Ruconest, and analyzed clinical responses after repeat administration of Ruconest. In this evaluation, no neutralizing antibodies against conestat alfa and plasma-derived C1-INH have been found. Furthermore, no effect on pharmacokinetics has been observed nor is there any indication of reduced efficacy following repeat administrations of Ruconest. Thus,

Important potential risk – Induction of acquired angioedema due to the formation of anti-C1-INH antibodies	
	there is no indication that neutralizing antibodies are being formed following treatment with Ruconest. A frequency cannot be determined because no neutralizing antibodies have yet been discovered.
Risk factors and risk groups	Risk groups or risk factors have not been identified.
Risk minimization measures	Routine risk minimization measures: *Not applicable* Additional risk minimization measures: *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk – Thromboembolic complications	
Evidence for linking the risk to the medicine	This risk is based on thrombogenicity position paper and data from post-marketing exposure. During off-label administration of very high doses of the plasma-derived C1-INH product Berinert (25 times higher than the recommended dose for an angioedema attack) in neonates who underwent cardiac surgery with extracorporeal circulation for major cardiovascular malformations, a concern about a possible risk for thromboembolic complications has arisen. Besides the surgical intervention, having a significant risk factor for thromboembolic complications, there is a theoretical concern of whether the thromboembolic complications observed in these cases are caused by C1-INH as C1-INH influences the fibrinolytic system. The position paper concluded that based on the observations on coagulation and fibrinolytic parameters in HAE patients treated with conestat alfa indicated no effect of conestat alfa on activation of coagulation and fibrinolysis in HAE patients at the doses administered. There has been one event of myocardial infarction in a 58-year-old patient participating in Study C1 1304. The event occurred more than 2 months following a single administration of 100 U/kg conestat alfa and was unlikely related to administration of conestat alfa according to the Investigator. The thromboembolic events reported from post-marketing setting included Pulmonary thrombosis, Pulmonary embolism, Device occlusion, Thrombosis, Subclavian vein thrombosis, Jugular vein thrombosis, Transient ischaemic attack, and Cerebrovascular accident which were all assessed as serious. Outcome was not reported in majority of the cases. A causal relationship cannot be established based on available data. To further support the Sponsor's position that the thromboembolic risk of Ruconest is negligible, a study was undertaken to assess the effects of

Important potential risk – Thromboembolic complications	
	Ruconest on activation of coagulation and of fibrinolysis in patients with HAE who participated in the randomized controlled phase of Study C1 1205 RCT and who received conestat alfa (50 or 100 U/kg of body weight) or saline for treatment of an acute attack. In the investigation Ruconest had no effect on coagulation and fibrinolysis parameters. A frequency cannot be determined. In one study with a plasma-derived C1-INH (Cinryze), with prophylactic use the incidence of such events was approximately 5%.
Risk factors and risk groups	Risk factors observed in patients who developed thrombotic and thromboembolic events following plasma-derived C1-INH treatment include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility.
Risk minimization measures	Routine risk minimization measures: *Not applicable*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk – Medication error	
Evidence for linking the risk to the medicine	This risk is based on post-marketing safety data. A frequency cannot be determined. Evaluation of the post-marketing safety data on medication errors including with or without associated AEs did not identify patterns of medication errors and/or potential medication errors suggestive of any new safety concerns.
Risk factors and risk groups	Lack of experience of the patient or caregiver could increase the risk of medication errors. Patients with decreased venous access will be at increased risk of injection errors.
Risk minimization measures	Routine risk minimization measures: *Not applicable* Additional risk minimization measures: *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk – Adverse event with self or home administration	
Evidence for linking the risk to the medicine	Most adverse event reports originate from the US. According to the US prescribing information, self-administration is allowed. Thus far, there are no data originating from the US suggesting an increased risk of adverse events with self-administration. Use of the self-administration within Europe is limited. The most serious adverse event with self-administration may be the potential of an air embolism when a large amount of bubbles or air is injected into the vein. Air bubbles may develop during reconstitution if the vial is agitated or shaken too vigorously. This is a theoretical risk since a small volume of bubbles or air is unlikely to constitute a safety risk (air embolism) upon intravenous administration. Review of the available post-marketing safety data showed that it was not always possible to identify whether Ruconest was given in a hospital or at home based on the available information. Besides, the reported serious events mainly concerned infusion site reaction such as application site acne/erythema, catheter site infection, and infusion site infection/pain. In most cases no outcome was reported. Overall, no air embolism has been reported.
Risk factors and risk groups	Lack of experience of the patient or caregiver could increase the risk of a medication error. Patients with decreased venous access will be at increased risk of injection site complication.
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.4* *PL section 3* Additional risk minimization measures: *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information – Data on pediatric patients aged 2 up to 5 years	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.2 and 4.4* *PL section 2*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information – Data on pregnant and breastfeeding women	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.6* *PL section 2* Additional risk minimization measures: *Educational materials for physicians and patients*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)* See Section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

Not applicable

II.C.2 Other studies in post-authorization development plan

Ruconest registry (Study C1 1412)

Purpose of the study: To observe adverse events and insufficient efficacy, and to assess the immunological profile following single and repeat treatment with Ruconest in patients diagnosed with HAE.

Effectiveness evaluation of educational materials for Ruconest

Purpose of the study: All healthcare professionals who are expected to prescribe Ruconest will be provided with an educational materials pack. Following 2 major revisions of the educational materials, Pharming Group N.V. was requested to study the effectiveness of these educational materials. The MAH will conduct a survey of prescribing physicians' knowledge and understanding of specific risks associated with Ruconest, as described in the Product Information (PI), and communicated to the healthcare professionals via these educational materials.

The main objectives of this study are:

- To evaluate the HCPs awareness of the need to take a careful history of rabbit allergy, the need for monitoring for hypersensitivity reactions and knowing what action to take as a measure of the effectiveness of the educational materials.
- To evaluate whether the patient and prescriber checklists, and patient diary have been useful in training patients to enable safe and effective use of Ruconest and whether key safety messages are understood by the prescriber and communicated to their patients as a measure of the effectiveness of the educational materials.

A secondary study objective of this study is to evaluate whether the reporting rate of adverse events related to hypersensitivity reactions after administration of Ruconest has changed (based on data from routine pharmacovigilance reporting and the EU registry).